Exhibit A

US008426450B1

(12) **United States Patent**
Fadini et al.

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(45) **Date of Patent: Apr. 23, 2013**

(54) **SUBSTITUTED 4-PHENYL PYRIDINES HAVING ANTI-EMETIC EFFECT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/478,361**

(22) Filed: **May 23, 2012**

Related U.S. Application Data

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**
A61K 31/44 (2006.01)

(52) **U.S. Cl.**
USPC **514/352**; 544/360; 546/304

(58) **Field of Classification Search** 514/352; 544/360; 546/364
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,985,856	A	11/1999	Stella et al.	
6,297,375	B1	10/2001	Bös et al.	
6,303,790	B1	10/2001	Hilpert et al.	
6,479,483	B2	11/2002	Bös et al.	
6,531,597	B2	3/2003	Hoffmann-Emery et al.	
6,593,472	B2	7/2003	Hoffmann et al.	
6,719,996	B2	4/2004	Kuentz et al.	
6,747,026	B2	6/2004	Hoffmann et al.	
6,806,370	B2	10/2004	Hoffmann et al.	
7,211,579	B2 *	5/2007	Funk et al	514/253.01

OTHER PUBLICATIONS

Kramer et al., "Distinct Mechanism for Antidepressant Activity by Blockade of Central Substance P Receptors." Science 281 (5383), 1640-1645 (1998).

Gesztesi et al., "Substance P (Neurokinin-1) Antagonist Prevents Postoperative Vomiting after Abdominal Hysterectomy Procedures." Anesthesiology 93 (4), 931-937 (2000).

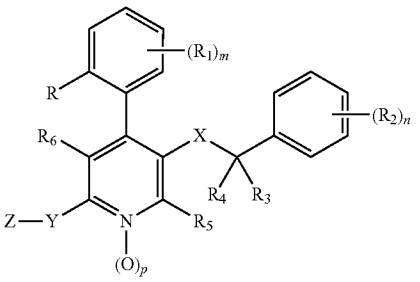
* cited by examiner

Primary Examiner — Douglas M Willis
(74) *Attorney, Agent, or Firm* — Arnall Golden Gregory LLP; Clark G. Sullivan

(57) **ABSTRACT**

Disclosed are compounds, compositions and methods for the prevention and/or treatment of diseases which are patho-physiologically mediated by the neurokinin (NK_1) receptor. The compounds have the general formula (I):

Formula (I)



3 Claims, No Drawings

SUBSTITUTED 4-PHENYL PYRIDINES HAVING ANTI-EMETIC EFFECT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 61/564,537, filed Nov. 29, 2011.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT

Not applicable.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC

Not applicable.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

2. Description of Related Art

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et al. (Science 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis. Gesztesi et al. (Anesthesiology 93(4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis

U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron (a $5\text{-}HT_3$ receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-Oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-Oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-Oxide derivatives are reported in the '026 patent.

U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives

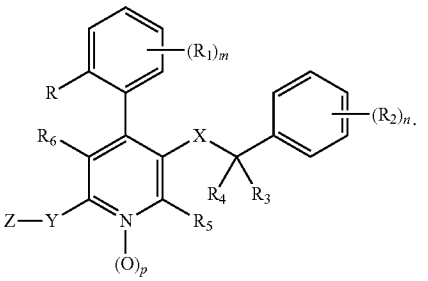
of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclosure how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as stability, local tolerance at the site of administration, bioavailability, metabolism or toxicity.

In view of the above, there is a need to find new derivatives of 4-phenyl-pyridine compounds that are effective NK_1 receptor antagonists, with enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives particularly well-suited for antagonizing the NK_1 receptor, having the following general formula (I):

Formula (I)



and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK_1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK_1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

DETAILED DESCRIPTION

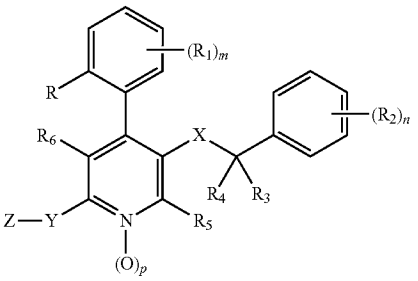
Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —$S(O)_2R^{102}$, —$SR^{101}S(O)_2NR^{101}R^{102}$, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

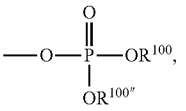
Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$-phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of

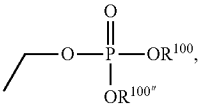
(Ia)

(Ib)

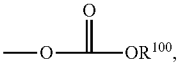
(Ic)



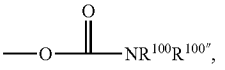
(Id)



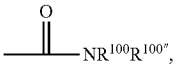
(Ie)



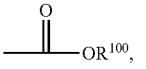
(If)



(Ig)

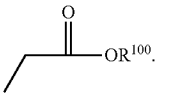


(Ih)



and

(Ii)



where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

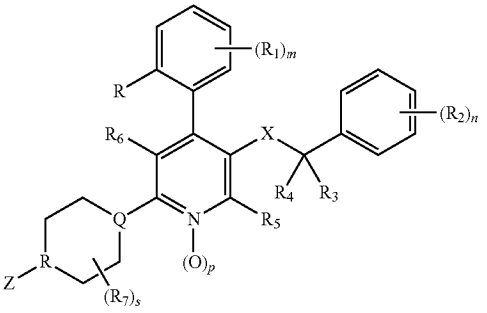
R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is from 0 to 4; n is from 0 to 5; p is from 0 to 1; and with a proviso that if a non-pyridine N-Oxide ($N^- \rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein X is —$NR^{101}C(O)$. In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

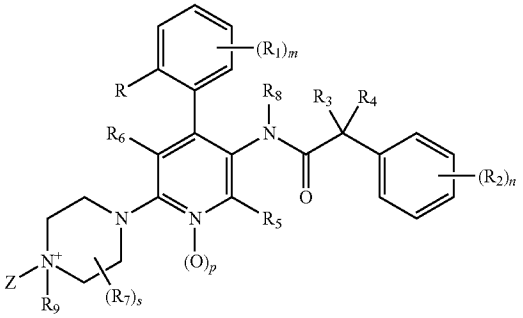
Formula (II)



where Q and R are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

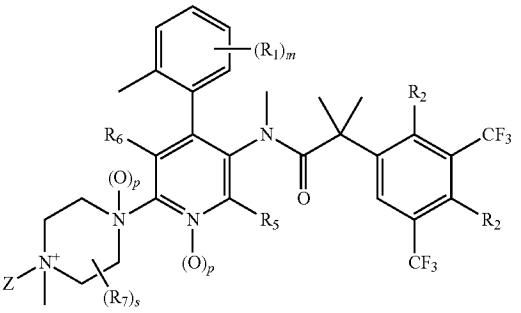
Formula (III)



Where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

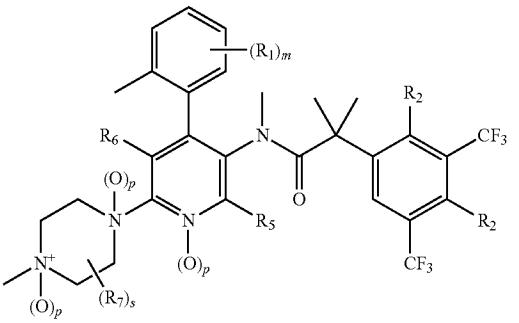
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

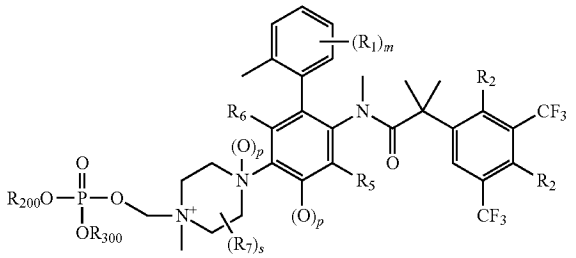
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

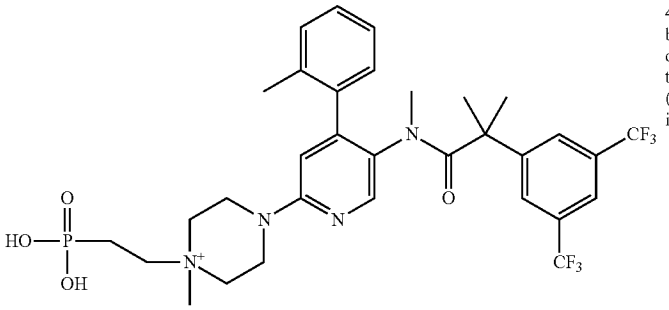
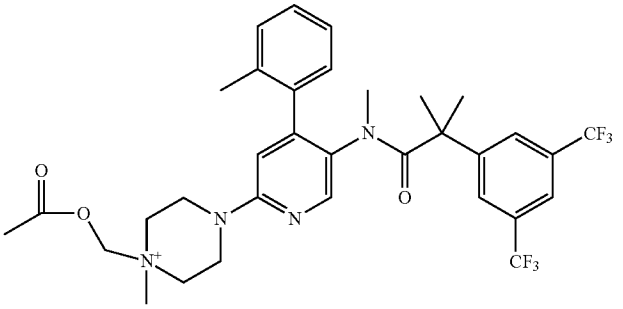
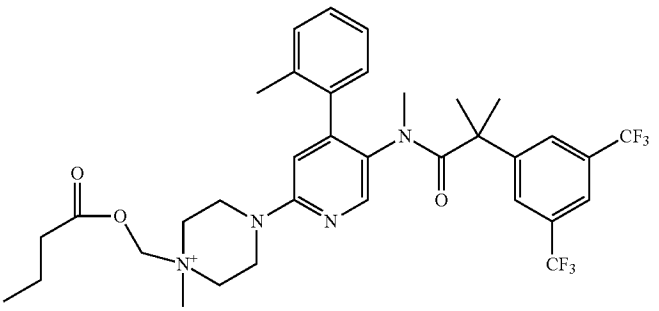
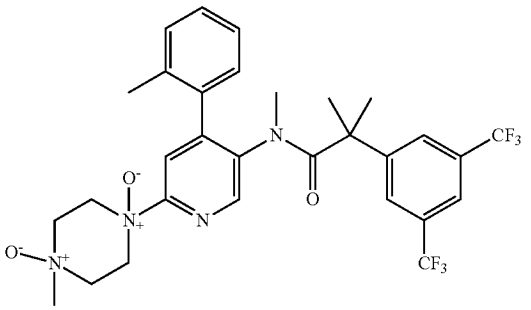
In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (VI):

Formula (VI)

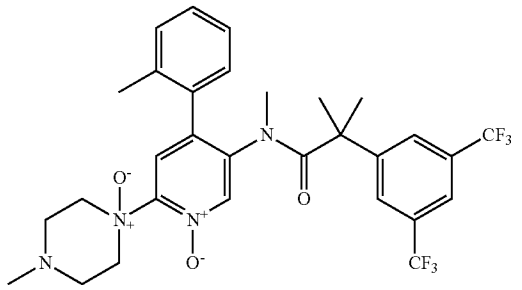
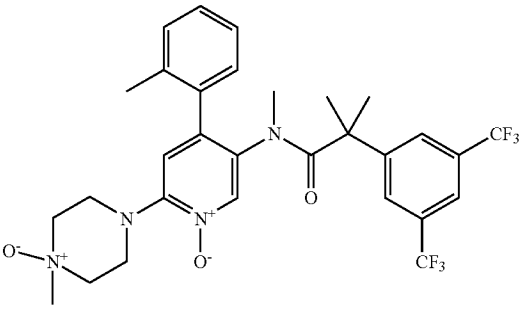
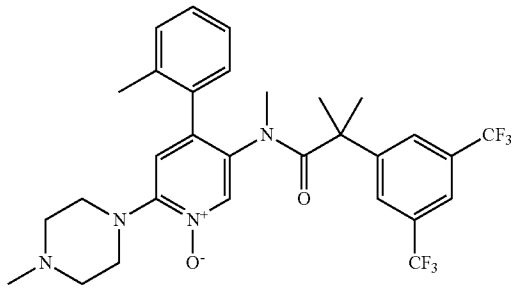
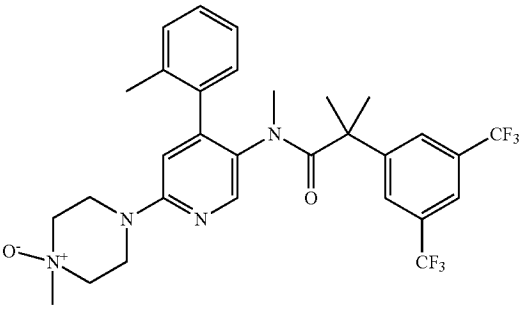


where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of:

GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,
GA2		1-(acetoxymethyl)-4 -(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,
GA3		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,
GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

-continued

GA5		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,
GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

1. Salts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric,

ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl(C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

2. General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006, which are hereby incorporated by reference. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

3. Definition of Terms

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms. In one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or ═O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or ═O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y—," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X-Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile")—CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The term "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula —$NH(CH_3)$), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to ═O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, prop oxyc arb onyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to ═S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxido" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfonyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring

atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane, thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, is opyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2— The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2— The term "methylenoxy" refers to the group —CH_2—O— The term "methylenethioxy" refers to the group —CH_2—S— The term "methylenamino" refers to the group —CH_2—N(H)— The term "ethylenoxy" refers to the group —CH_2—CH_2—O— The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halo-

gen, and cyano do not fall within this definition. If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule.

If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

B. Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active compounds and compositions, for example, can be administered orally, rectally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

In some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

A. Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide$\geqq$1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg. orally on day 1, followed by 8 mg. orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously administered at a dosage of from about 10 mg to about 200 mg, from

about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-day course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said 5-HT_3 antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg, or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 mL.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodiment, the netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease. In some other forms, disclosed are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

B. More Definitions of Terms

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

1. A, An, The

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and

specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

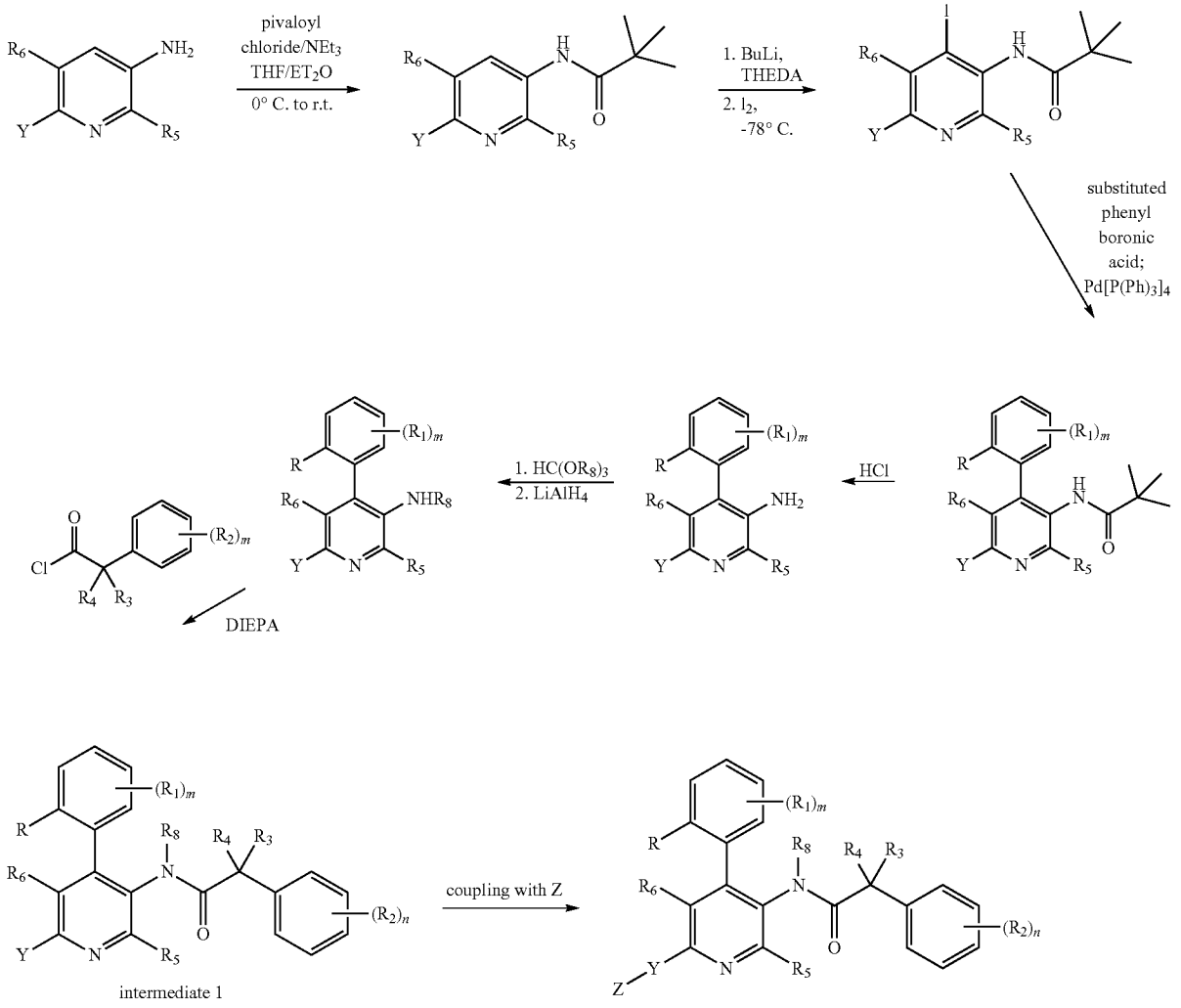
A. Example 1

1. Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

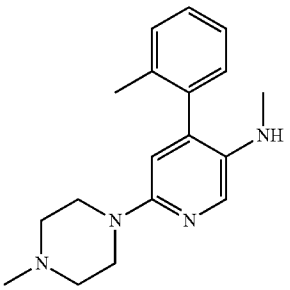
General Scheme of Preparing Compounds of Formula (I)

Scheme 1



Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, the entirety of which are incorporated herein by reference.

Synthesis of methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THF were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolylmagnesium chloride solution (1M in THF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THF removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent: ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution. The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THF were added 3.1 ml (42.0 mMol) thionylchloride and 143. mu.l (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0° C. After 30 minutes at 0° C., THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as a beige crystalline foam. MS (ISP): 247 ($M+H^+$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamide in 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam. MS (ISP): 311 ($M+H^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol 4:1) to yield 100 mg (70%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 ($M+H^+$, 100), 226 (42).

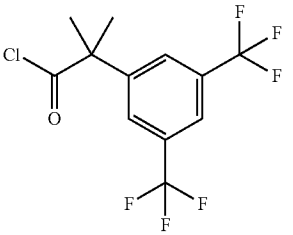
Step 5:

2.15 ml (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH=8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam. MS (ISP): 341 ($M+H^+$, 100), 284 (35).

Step 6:

A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-Al® (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 ($M+H^+$, 100).

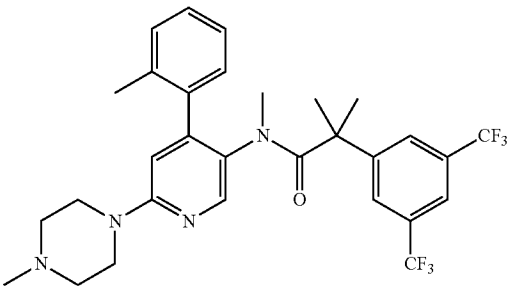
Synthesis of 2-(3,5-bis-Trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution was rotary evaporated to dryness. 9 ml Toluene were added

and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, $3H_{arom}$); 1.77 (s, 6H, 2 CH_3).

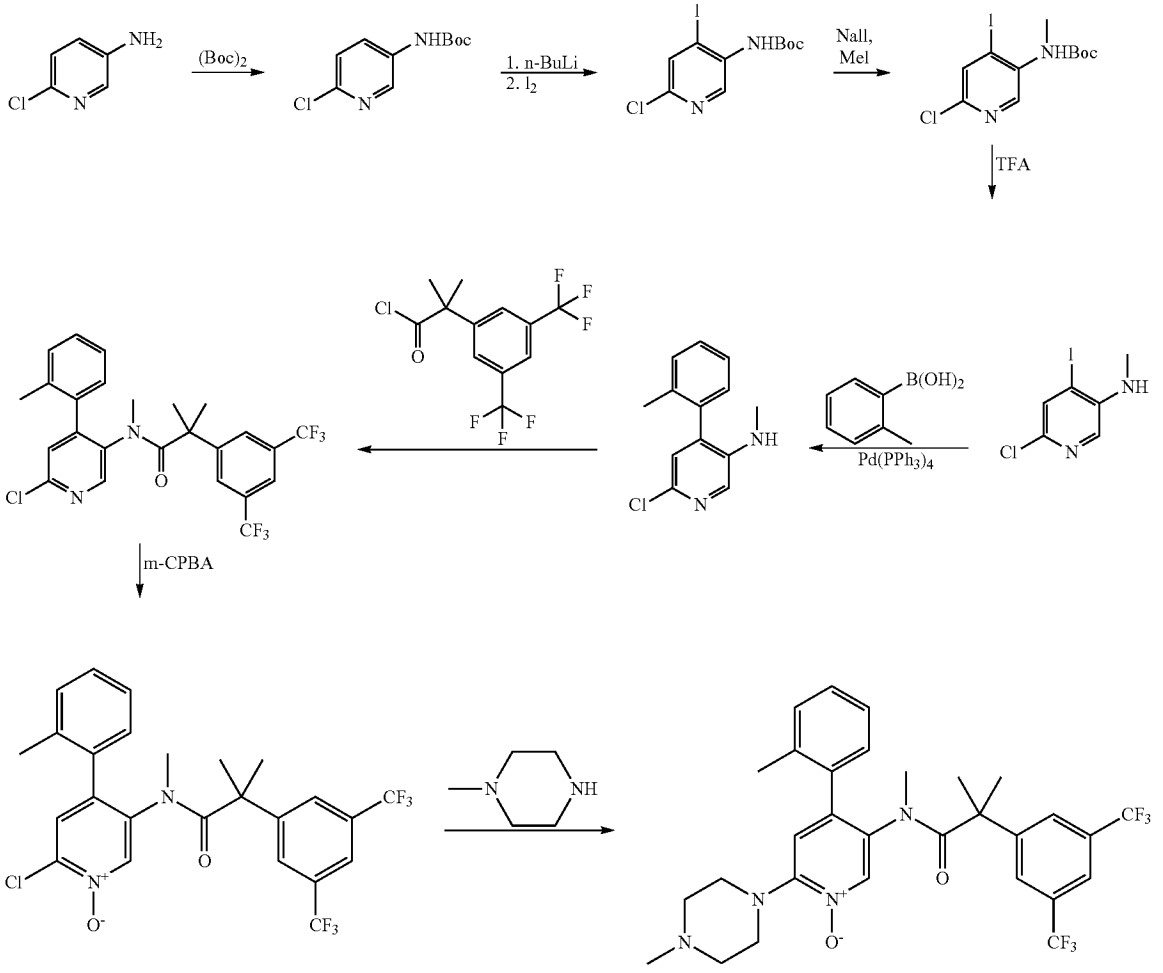
Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)



A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol)-2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide as white crystals. M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-3,5-bis(trifluoromethyl)phenyl)-N, 2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2



Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl (6-chloropyridin-3-yl)carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl (6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THF was added n-BuLi (600 mL, 1.5 mol) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THF was added. Then the solution was stirred at −78° C. for 4 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl (6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 mL of anhydrous THF was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THF was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl (6-chloro-4-iodopyridin-3-yl)(methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 mL of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol). The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under N_2 atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

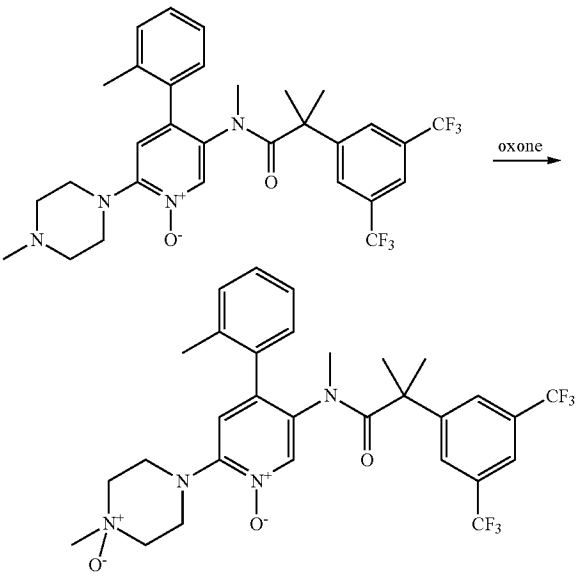
To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature. 1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45-1.20 (m, 6H).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl) pyridin-2-yl)-1-methylpiperazine 1-oxide

Scheme 3

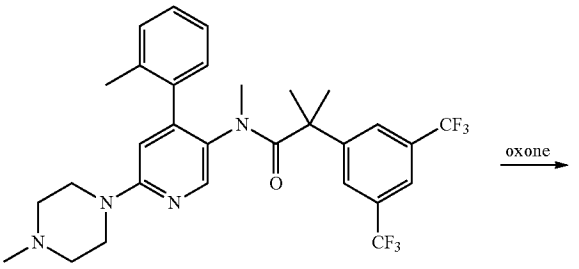


To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 mL of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for

4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37-7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 2H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

Scheme 4



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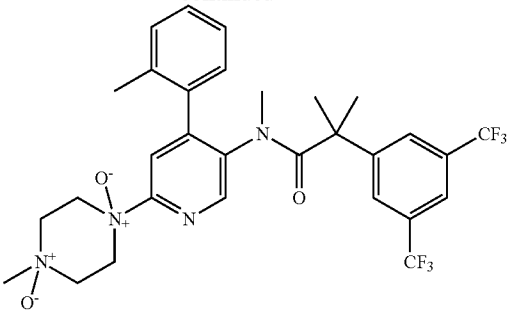
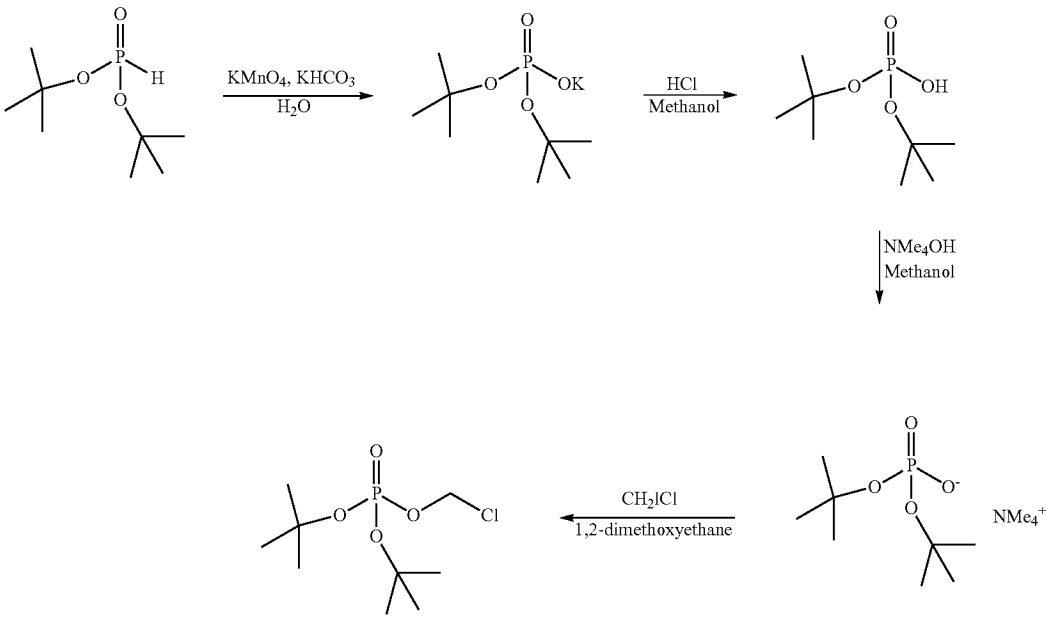


To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (3.38 g, 40.3 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR ($CDCl_3$, 400 MHz, at 333K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26-7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

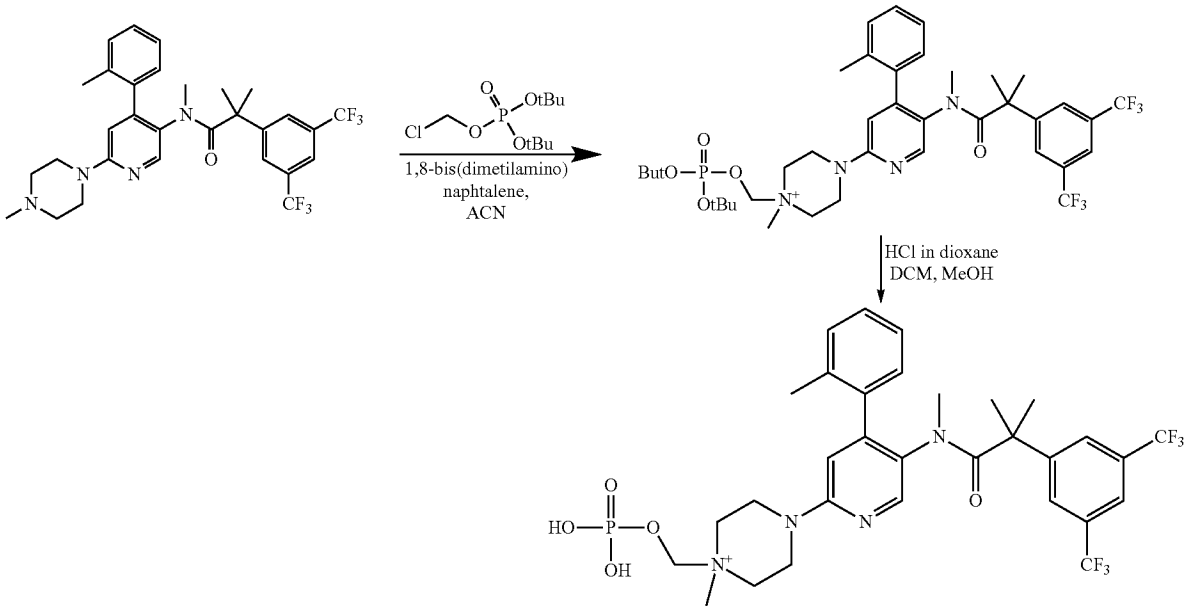
Synthesis of di-tert-butyl(chloromethyl)phosphate

Scheme 5



Di-tert-butyl phosphohite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time. The reaction as then allowed to continue at room temperature for an additional half hour. Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the crude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloroiodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis (trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium without further purifications (60% yield): ^{1H}NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium



The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile. 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphtalene and 46.6 g (80.54 mmole) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropylether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropylether/acetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4-(5-{2-[3,5-bis (trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[bis(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-7.10 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m. 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[bis(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and

pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium as white solid (Yield: 88-93%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

2. Evaluation of Representative Compounds of Formula (I)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 1 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE 1

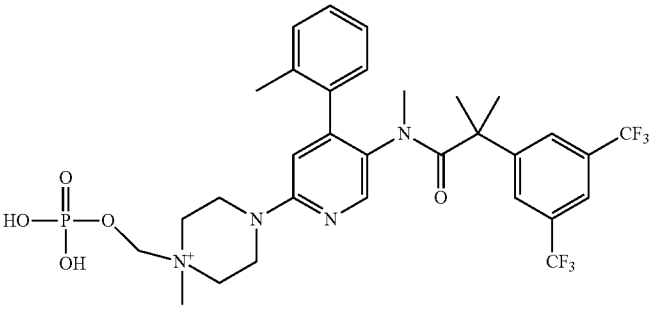
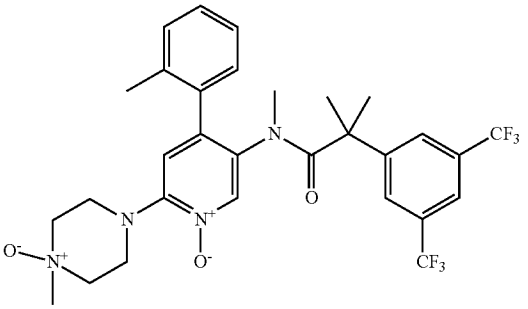
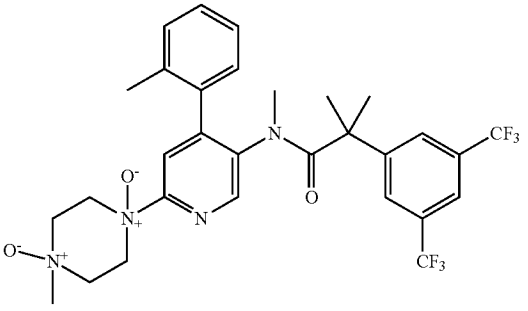
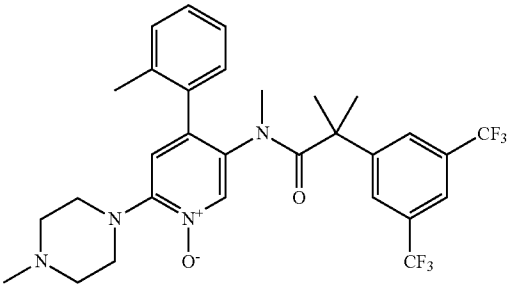
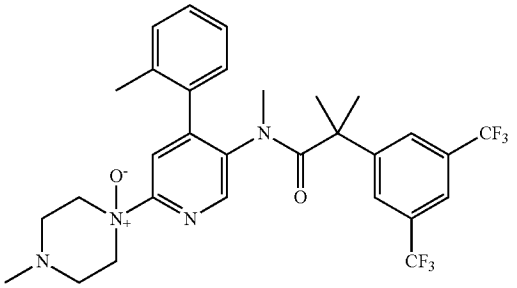
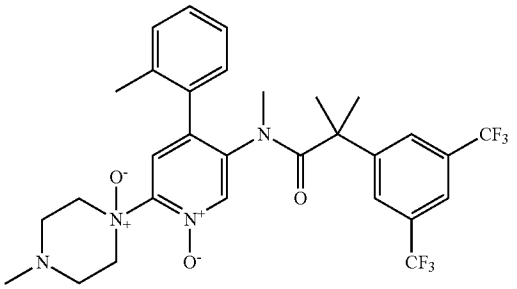
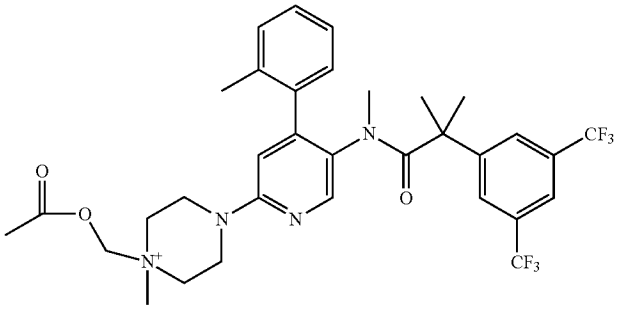
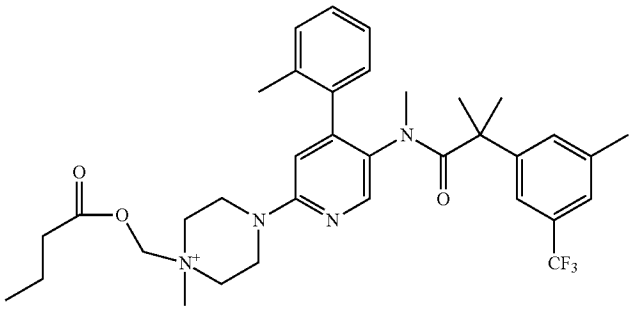
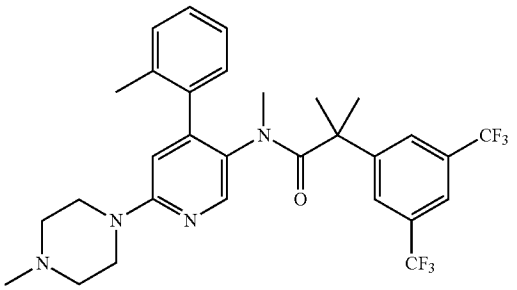
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1	 as produced in paragraph 141.	medium	10-15 mg/ml
2		high	>10 mg/ml
3		high	>10 mg/ml
4		medium	~0.6 mg/ml

TABLE 1-continued

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
5*		medium	~1 mg/ml
6		low	N/A
7		low	insoluble
8		Low	insoluble
9*			0.25

*Reference Compound

ii. Local Tolerance

In contrast to netupitant, seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

There were minimal signs of inflammation at injection site and there was little edema;

No later stage thrombus was found in any animal studied;

Severity of inflammation was similar in compound and vehicle-treated animals;

No tissue necrosis was observed in any of the tails; and

The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 1), as compared to a reference compound—netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a dose volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal Before administration, rats were fasted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pre-dose and at 0.05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO: Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solubility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (IV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, 15 and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC. MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 1, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 2:

Table 1

TABLE 1

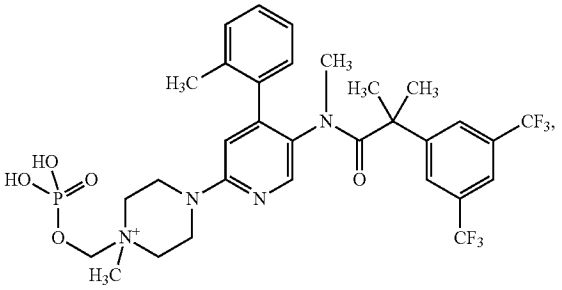
	IV			
	Comp. No. 1	Comp. No. 2	Comp. No. 3	PO Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng · min/ml)	315627	88732	192730	307285
Bioequivalence (%)	103	29	63	

*Reference Compound

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

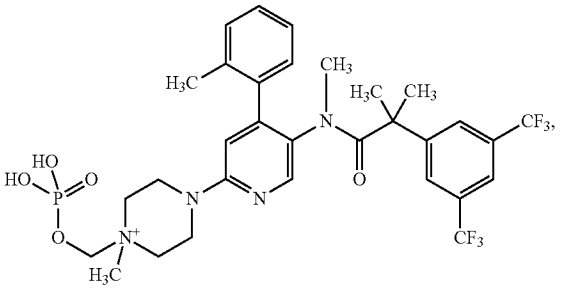
1. The compound:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim **1**, and one or more pharmaceutically acceptable excipients.

3. A compound selected from the group consisting of:



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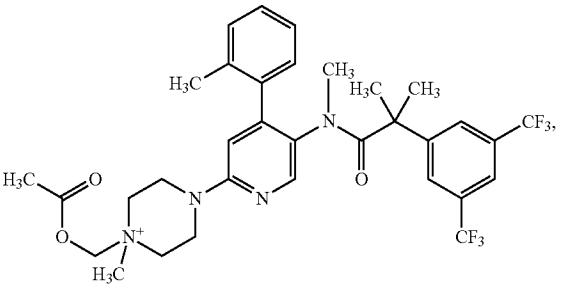
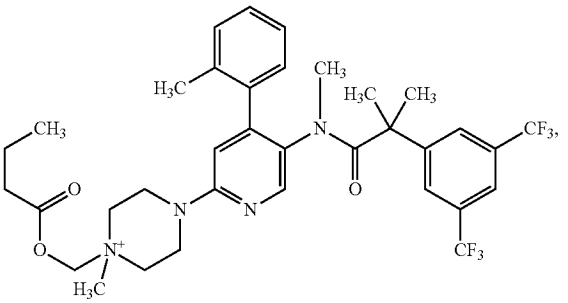


and



or a pharmaceutically acceptable salt thereof.

* * * * *

Exhibit B

US008895586B2

(12) **United States Patent**
Fadini et al.

(10) **Patent No.: US 8,895,586 B2**
(45) **Date of Patent: Nov. 25, 2014**

(54) **METHODS OF TREATING EMESIS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/864,381**

(22) Filed: **Apr. 17, 2013**

(65) **Prior Publication Data**

US 2013/0231315 A1 Sep. 5, 2013

Related U.S. Application Data

(62) Division of application No. 13/478,361, filed on May 23, 2012, now Pat. No. 8,426,450.

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**

A61K 31/444	(2006.01)
A61K 31/497	(2006.01)
C07D 213/02	(2006.01)
C07D 401/04	(2006.01)
A61K 31/44	(2006.01)
C07D 213/89	(2006.01)
A61K 31/496	(2006.01)
A61K 31/56	(2006.01)
C07D 213/74	(2006.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 213/74*** (2013.01); ***A61K 31/44*** (2013.01); ***C07D 213/89*** (2013.01); ***C07D 401/04*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 45/06*** (2013.01)

USPC **514/336**; 514/253.01; 544/360; 546/309

(58) **Field of Classification Search**

CPC . A61K 31/444; A61K 31/497; C07D 213/02; C07D 401/04

USPC 514/253.01, 336; 544/360; 546/309

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,985,856	A	11/1999	Stella et al.
6,297,375	B1	10/2001	Bös et al.
6,303,790	B1	10/2001	Hilpert et al.
6,479,483	B2	11/2002	Bös et al.
6,531,597	B2	3/2003	Hoffmann-Emery et al.
6,593,472	B2	7/2003	Hoffmann et al.
6,719,996	B2	4/2004	Kuentz et al.
6,747,026	B2	6/2004	Hoffmann et al.
6,806,370	B2	10/2004	Hoffmann et al.

OTHER PUBLICATIONS

Kramer et al., "Distinct Mechanism for Antidepressant Activity by Blockade of Central Substance P Receptors." Science 281 (5383), 1640-1645 (1998).

Gesztesi et al., "Substance P (Neurokinin-1) Antagonist Prevents Postoperative Vomiting after Abdominal Hysterectomy Procedures." Anesthesiology 93 (4), 931-937 (2000).

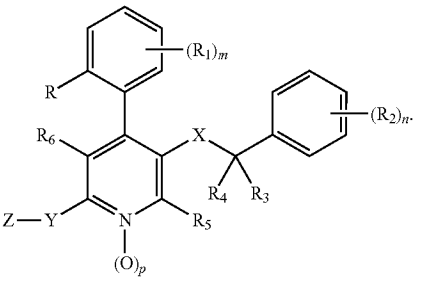
Primary Examiner — Douglas M Willis

(74) *Attorney, Agent, or Firm* — Clark G. Sullivan; Troutman Sanders LLP

(57) **ABSTRACT**

Disclosed are compounds, compositions and methods for the prevention and/or treatment of diseases which are patho-physiologically mediated by the neurokinin (NK_1) receptor. The compounds have the general formula (I):

Formula (I)



21 Claims, No Drawings

METHODS OF TREATING EMESIS

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 61/564,537, filed Nov. 29, 2011.

FIELD OF THE INVENTION

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

BACKGROUND

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et. al. (*Science* 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis, Gesztesi et al. (*Anesthesiology* 93 (4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis

U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron 5-HT_3 receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-Oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-Oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-Oxide derivatives are reported in the '026 patent.

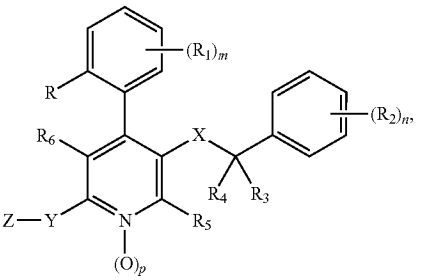
U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclosure how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as stability, local tolerance at the site of administration, bioavailability, metabolism or toxicity.

In view of the above, there is a need to find new derivatives of 4-phenyl-pyridine compounds that are effective NK_1 receptor antagonists, with enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives particularly well-suited for antagonizing the NK_1 receptor, having the following general formula (I):

Formula (I)



and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK_1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK_1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

DETAILED DESCRIPTION

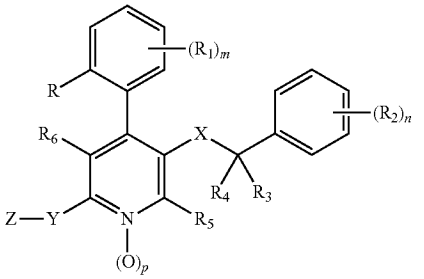
Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl,

halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —S(O)2R^{102}, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —C(O)$NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

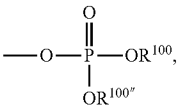
Z is a structural formula selected from the group consisting of

(Ia)

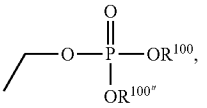
(Ib)

-continued

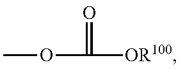
(Ic)



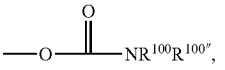
(Id)



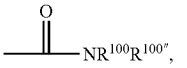
(Ie)



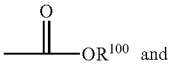
(If)



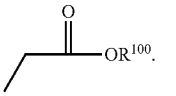
(Ig)



(Ih)



(Ii)



where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —C(O)$NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroalylalkyl;

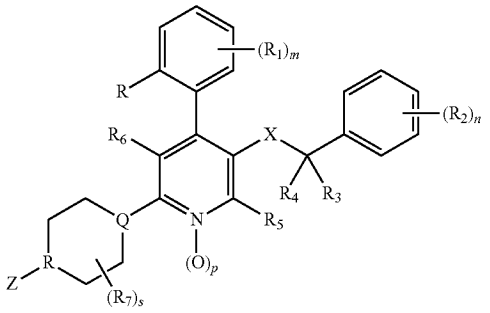
m is from 0 to 4; n is from 0 to 5; p is from 0 to 1, and with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically accept-

able salts or adducts thereof, wherein X is —$NR^{101}C(O)$. In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

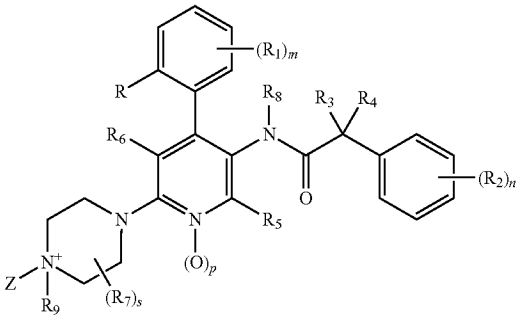
Formula (II)



where Q and R are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

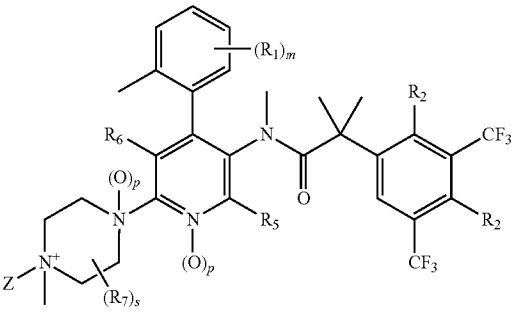
Formula (III)



Where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

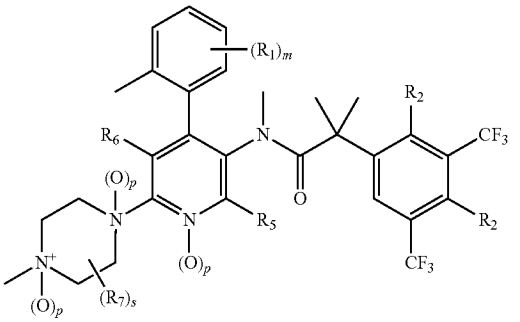
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

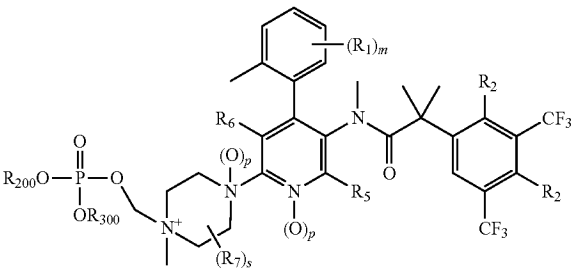
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

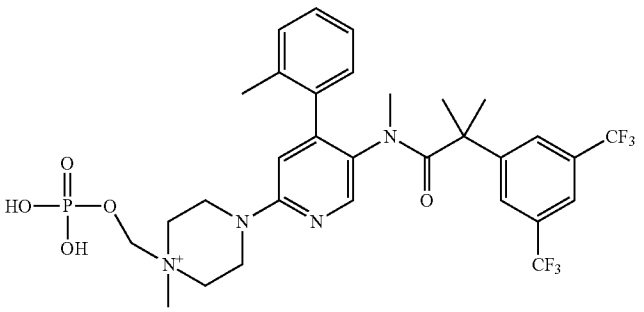
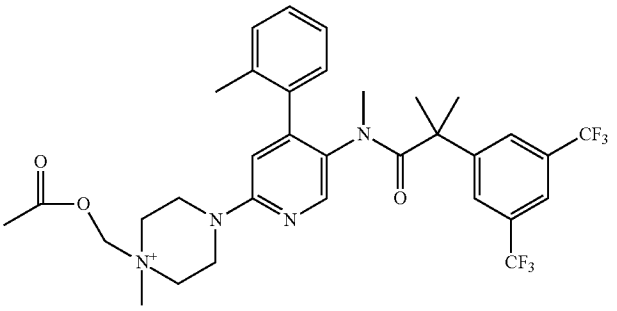
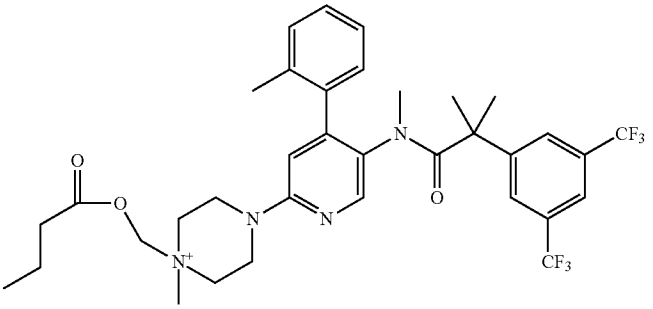
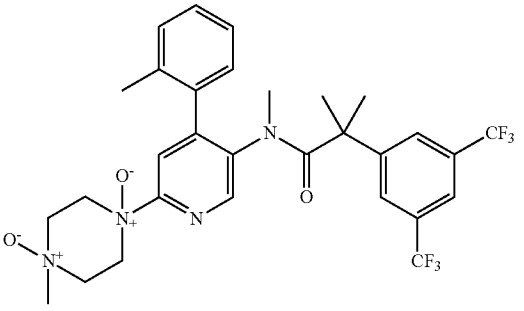
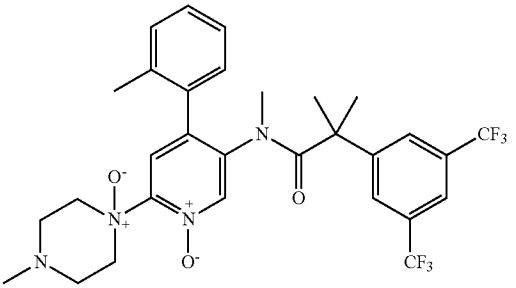
In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound. of formula (I) has a structure of formula (VI):

Formula (VI)

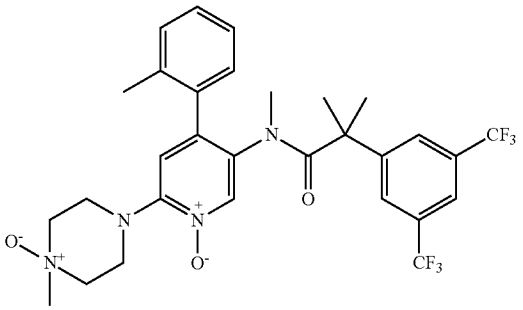
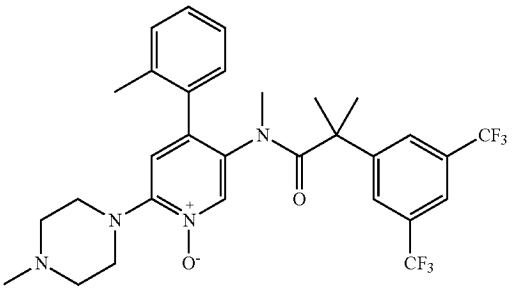
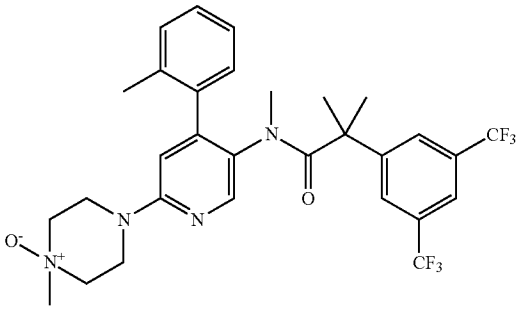


where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of:

GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,
GA2		1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,
GA3		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-(butyryloxy)methyl)-1-methylpiperazin-1-ium,
GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,
GA5		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

-continued

GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

1. Salts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil, In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfanate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

2. General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006, which are hereby incorporated by reference. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

3. Definition of Terms

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyi and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "F" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms. In one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each hound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms, Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl

and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group, When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y-," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon Atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X—Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile") —CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The tem "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula —NH(CH_3)), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine, in another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to =O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarhonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to =S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxido" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsuifinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered

heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each hound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, beuzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophertyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, isothiazolinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-thazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6oxazinyl (also known as "pentoxazolyl"), 1,2,6oxazinyl, of 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopynolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazlnyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10}cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2—. The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2—. The term "methylenoxy" refers to the group —CH_2—O—. The term "methylenethioxy" refers to the group —CH_2—S—. The term "methylenamino" refers to the group —CH_2—N(H)—. The term "ethylenoxy" refers to the group —CH_2—CH_2—O—. The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. If a substituent is described. as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule.

If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

B. Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active compounds and compositions, for example, can be administered orally, rec-

tally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

in some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

A. Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of

whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg, orally on day 1, followed by 8 mg, orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously administered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 12.5 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-day course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day, in sonic other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said 5-HT_3 antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg, or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 mL.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl)phenyD-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodiment, the

netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease. In some other forms, disclosed are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

B. More Definitions of Terms

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

1. A, an, the

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities,

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual, Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

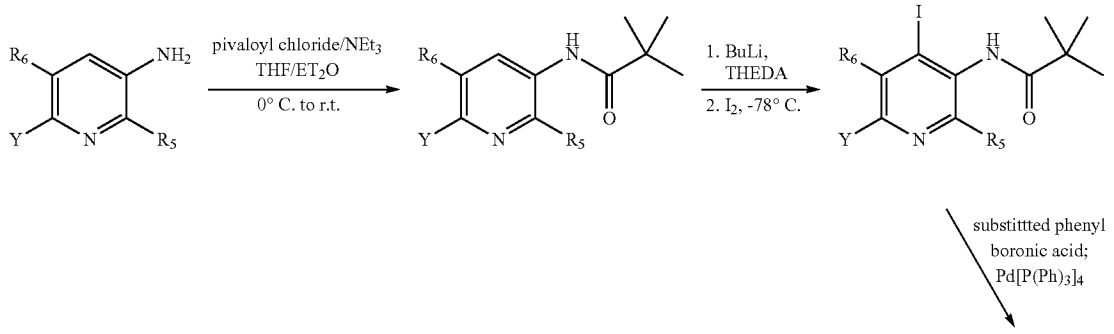
A. Example 1

1. Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

General Scheme of Preparing Compounds of Formula (I)

Scheme 1



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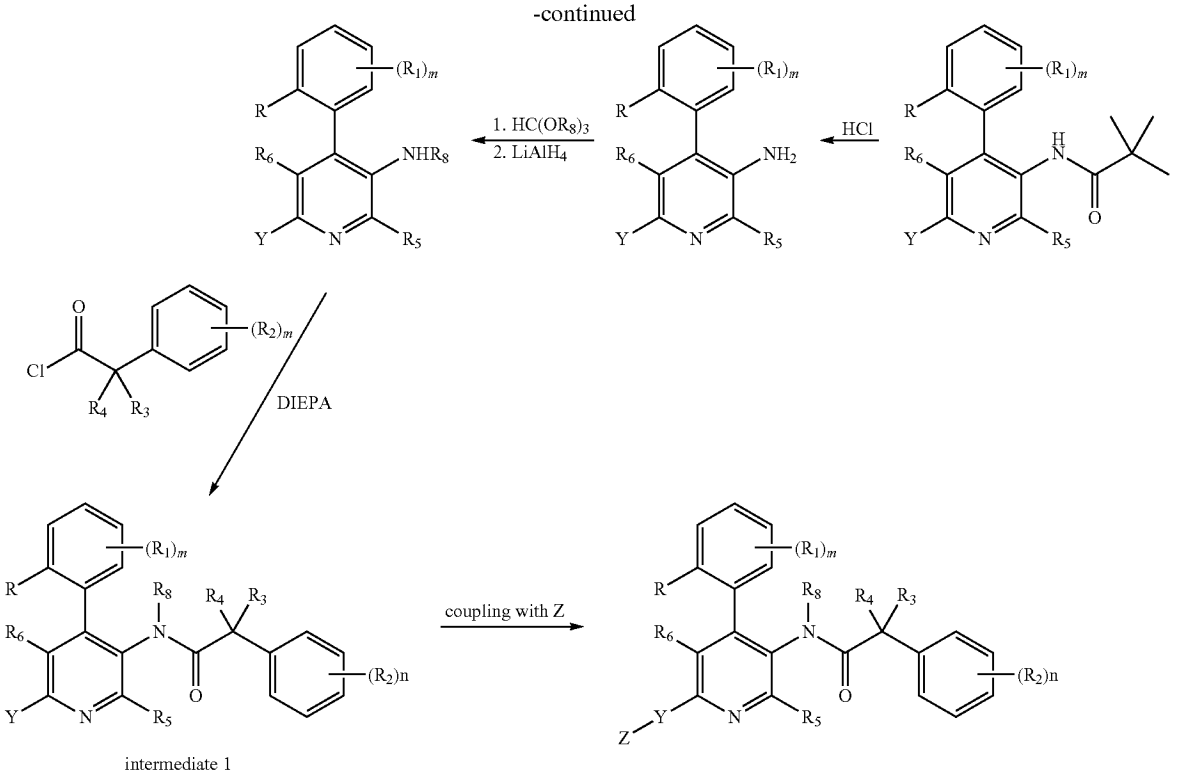
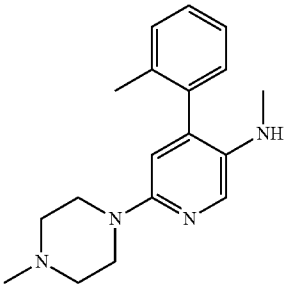


Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, the entirety of which are incorporated herein by reference.

Synthesis of methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THF were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolylmagnesium chloride solution (1M in THF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THF removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent: ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution, The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THF were added 3.1 ml (42.0 mMol) thionylchloride and 143 .mu.l (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0"C. After 30 minutes at 0° C., THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as a beige crystalline foam. MS (ISP): 247 ($M+H^{30}$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamidein 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam. MS (ISP): 311 ($M+H^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined. organic extracts were dried

(Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol 4:1) to yield 100 mg (70%) 6-(4-methyl-piperazine-1-yl)-4o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 ($M+H^+$, 100), 226 (42).

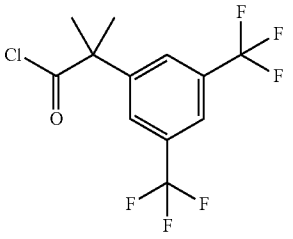
Step 5:

2.15 ml (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH=8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic, extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam. MS (ISP): 341 ($M+H^+$, 100), 284 (35).

Step 6:

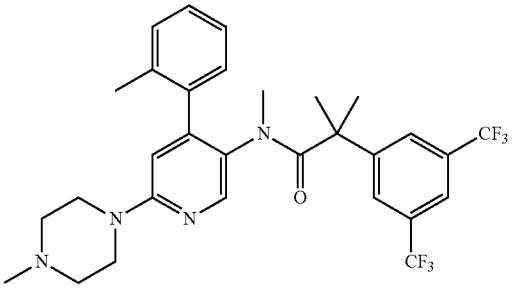
A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-Al.RTM. (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 ($M+H^+$, 100).

Synthesis of 2-(3,5-bis-Trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution was rotary evaporated to dryness. 9 ml Toluene were added and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, 3 H_{arom}); 1.77 (s, 6H, 2 CH_3).

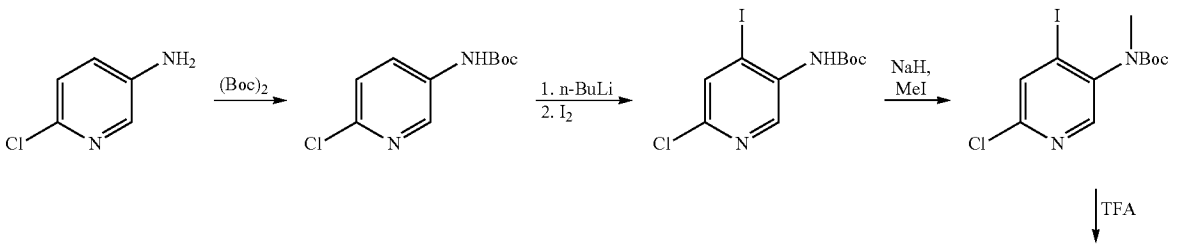
Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)



A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol)2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane, The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1yl)-4-(o-tolyl)pyridin-3yl)propanamide as white crystals. M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-(3,5-bis(trifluoromethyl)phenyl-N, 2-dimethylpropanamido)-2-(4-methylpiperazin-1yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2



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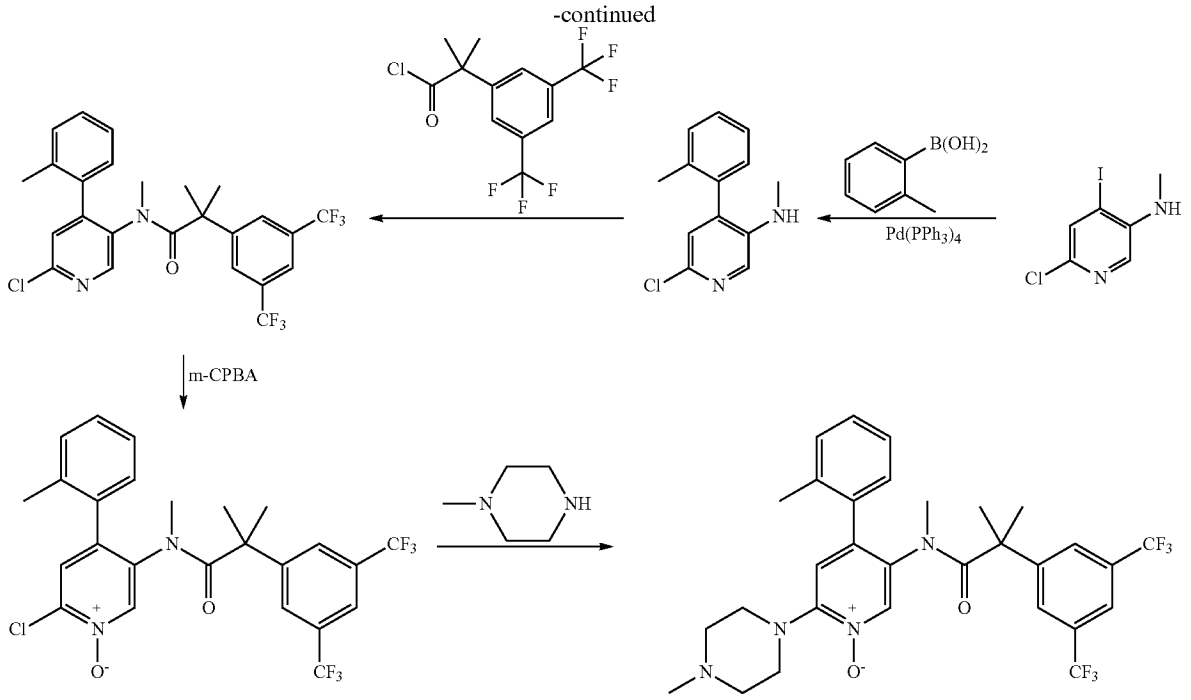


Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl (6-chloropyridin-3yl)carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl (6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THF was added n-BuLi (600 mL, L5 ml) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THF was added. Then the solution was stirred at −78° C. for 4 hrs, TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl (6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 of anhydrous THF was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THF was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl (6-chloro-4-iodopyridin-3-yl)methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 mL of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol), The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under N_2 atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried. over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(4-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

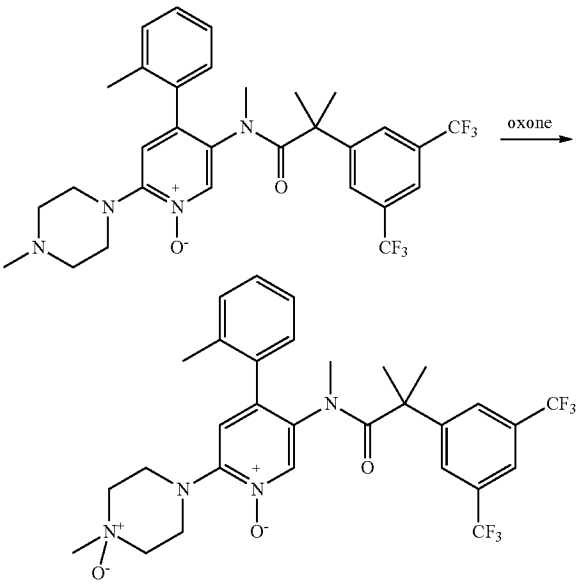
To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature. 1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA. and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl-N,2-dimethylpropanamido)-2-chloro-4(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%), ^{1}HNMR (CDCl3, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45~1.20 (m, 6H).

Synthesis of 4-(5(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamide)-1oxido-4-(o-tolyl)pyridin-2)-1-methylpiperazine-1-oxide

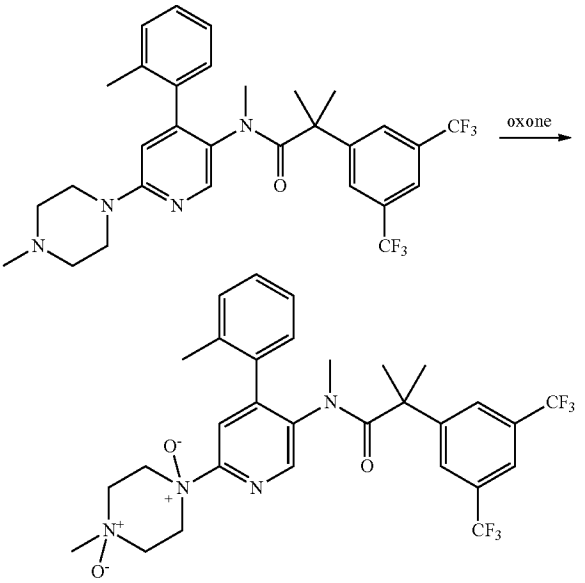
Scheme 3



To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 mL of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for 4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethy)phenyl)-N,2-dimethylpropanamido)-1-oxide-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37~7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 2H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4methylpiperazine 1,4-dioxide

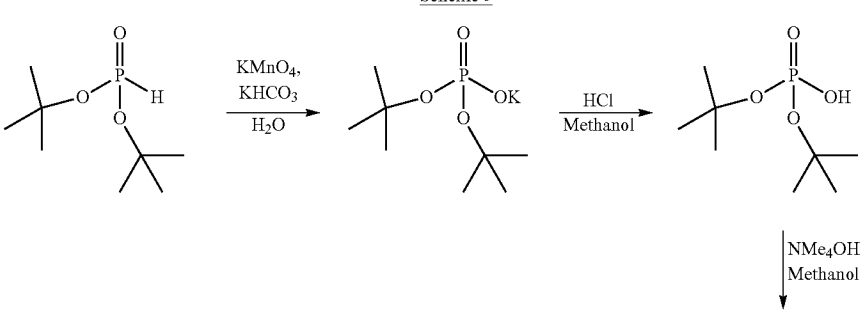
Scheme 4



To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (338 g, 403 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR (CDCl3, 400 MHz, at 333K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26~7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

Synthesis of di-tert-butyl (chloromethyl) phosphate

Scheme 5



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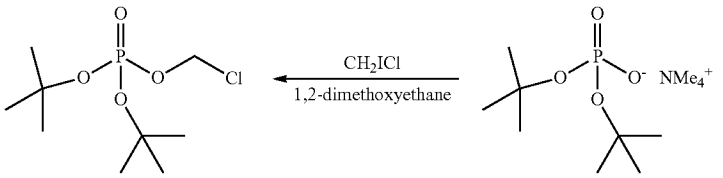
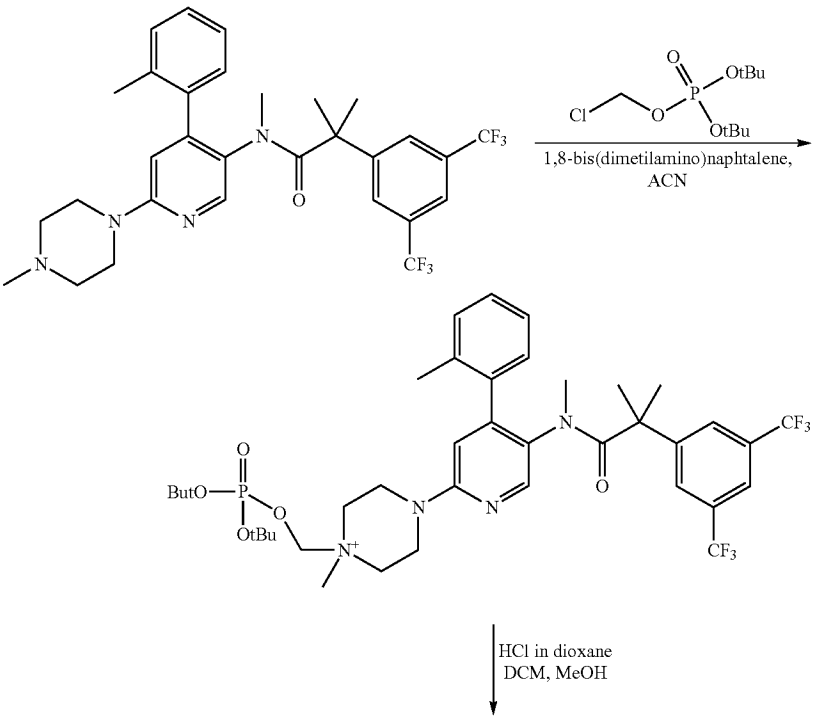


Di-tert-butyl phospohite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time, The reaction as then allowed to continue at room temperature for an additional half hour, Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C., a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the elude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloroiodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis (trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium without further purifications (60% yield): ^{1H}NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H, 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1 P).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium

Scheme 6



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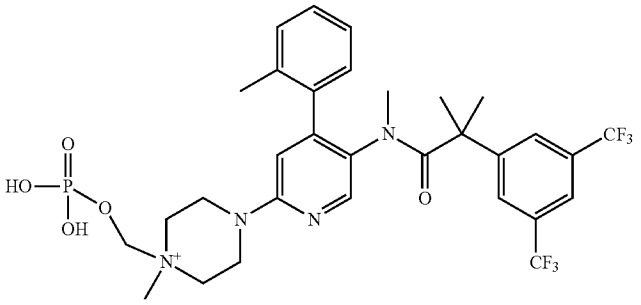


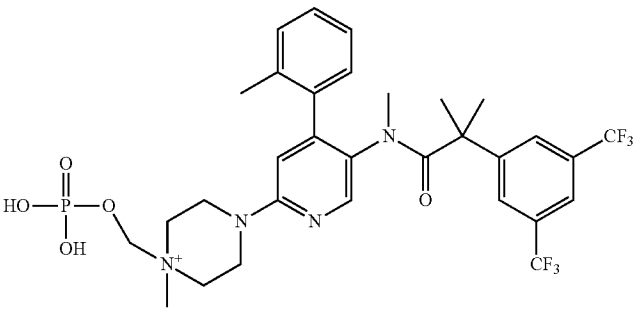
The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile, 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphthalene and 46.6 g (80.54 mmole) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropylether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropyletherlacetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4(5-{2-[3,5-bis (trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[bis(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-710 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m. 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamid}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[bis(tert-butoxy) phosphoryl]oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium as white solid (Yield: 88-93%), ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 HZ).

2. Evaluation of Representative Compounds of Formula (1)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 1 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE I

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1		medium	10-15 mg/ml

as produced in paragraph 141.

TABLE I-continued

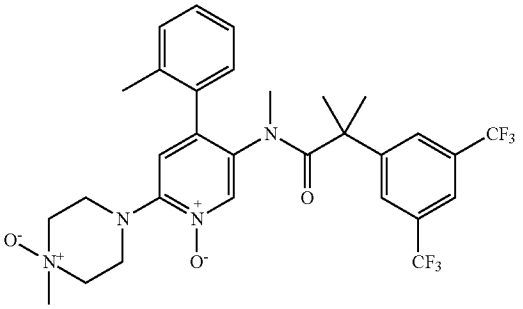
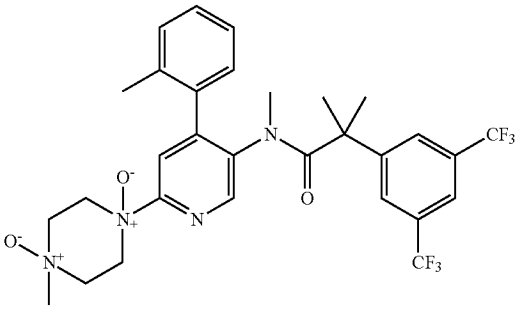
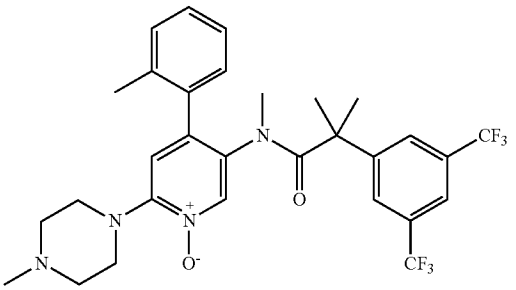
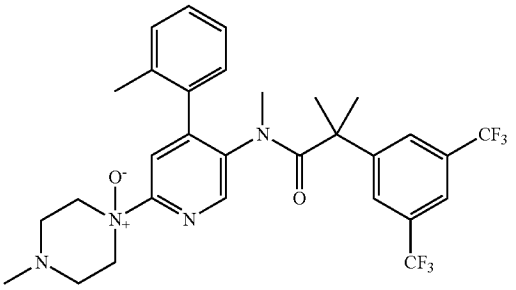
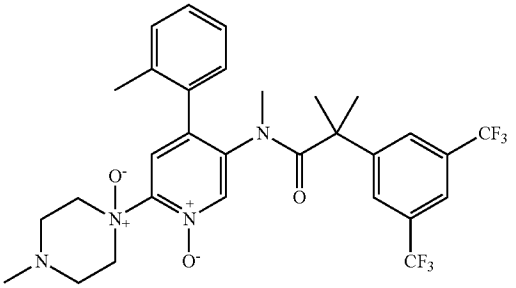
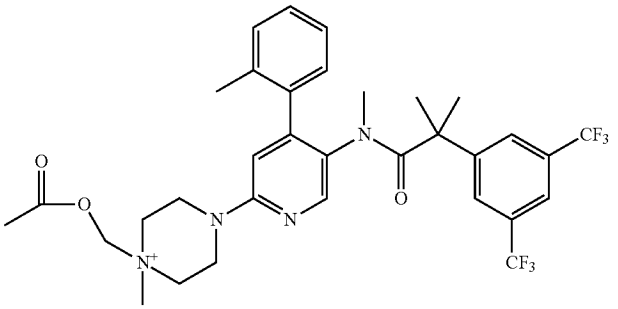
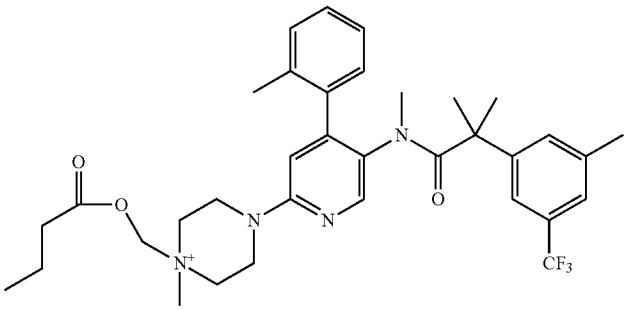
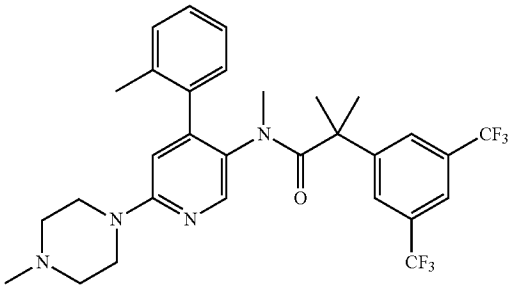
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
2		high	>10 mg/ml
3		high	>10 mg/ml
4		medium	~0.6 mg/ml
5 *		medium	~1 mg/ml
6		low	N/A

TABLE I-continued

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
7		low	insoluble
8		Low	insoluble
9 *			0.25

* Reference Compound

ii. Local Tolerance

In contrast to netupitant, seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

- There were minimal signs of inflammation at injection site and there was little edema;
- No later stage thrombus was found in any animal studied;
- Severity of inflammation was similar in compound and vehicle-treated animals;
- No tissue necrosis was observed in any of the tails; and
- The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 1), as compared to a reference compound netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a dose volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Before administration, rats were fluted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pro-dose and at 0,05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma

samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO:Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solubility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (IV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS), 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, 15 and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC. MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 1, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 2:

TABLE 2

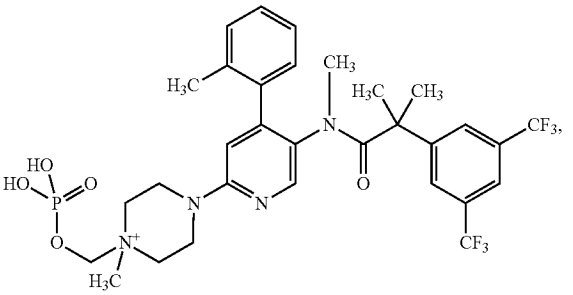
	IV			PO
	Comp. No. 1	Comp. No. 2	Comp. No. 3	Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng · min/ml)	315627	88732	192730	307285
Bioequivalence (%)	103	29	63	

*Reference Compound

Throughout this application, various publications are referenced, The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method of treating emesis in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the following compound:



or a pharmaceutically acceptable salt thereof.

2. The method of claim **1**, wherein said emesis comprises chemotherapy-induced nausea and vomiting, radiotherapy-induced nausea and vomiting, or post-operative nausea and vomiting.

3. The method of claim **1**, wherein said emesis is induced by moderately emetogenic chemotherapy.

4. The method of claim **1**, wherein said emesis is induced by highly emetogenic chemotherapy.

5. The method of claim **1**, wherein said emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy.

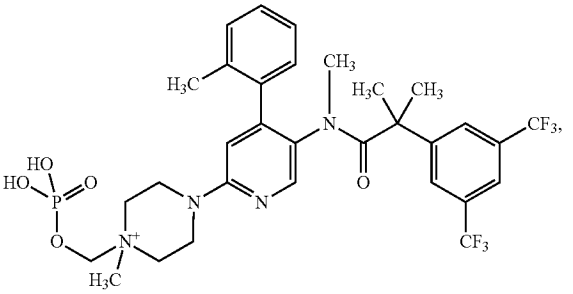
6. The method of claim **1**, wherein said compound is administered via injection.

7. The method of claim **1**, wherein said compound is administered at a dosage of from 10 to 200 mg.

8. The method of claim **1**, further comprising administering palonosetron or a pharmaceutically acceptable salt thereof.

9. The method of claim **1**, further comprising administering palonosetron or a pharmaceutically acceptable salt thereof and dexamethasone.

10. A method of treating emesis in a patient in need thereof, comprising administering to said patient via injection a therapeutically effective amount of the following compound:



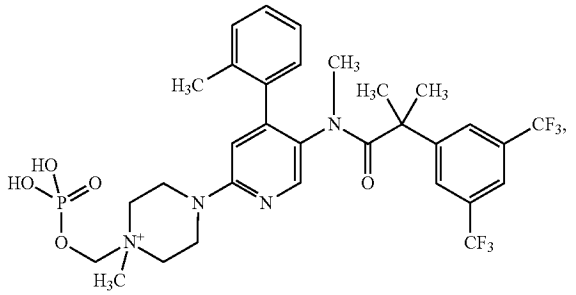
or a pharmaceutically acceptable salt thereof.

11. The method of claim **10**, wherein said emesis comprises chemotherapy-induced nausea and vomiting.

12. The method of claim **10**, wherein said emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy.

13. The method of claim **10**, wherein said compound is administered via injection at a dosage of from 10 to 200 mg.

14. A method of treating emesis in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the following compound:



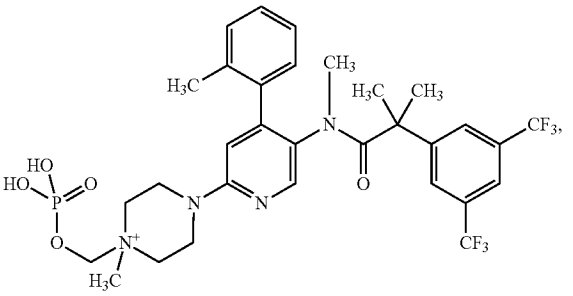
in combination with palonosetron or a pharmaceutically acceptable salt thereof and dexamethasone.

15. The method of claim **14**, wherein said emesis comprises chemotherapy-induced nausea and vomiting.

16. The method of claim **14**, wherein said compound is administered via injection.

17. The method of claim **14**, wherein said compound is administered via injection at a dosage of from 10 to 200 mg.

18. A method of treating emesis in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the following compound:



or a pharmaceutically acceptable salt thereof.

19. The method of claim **18**, wherein said compound is administered via injection.

20. The method of claim **18**, wherein said compound is administered at a dosage of from 10 to 200 mg.

21. The method of claim **18**, further comprising administering palonosetron or a pharmaceutically acceptable salt thereof.

* * * * *

Exhibit C

US009186357B2

(12) **United States Patent**
Trento et al.

(10) **Patent No.: US 9,186,357 B2**
(45) **Date of Patent: *Nov. 17, 2015**

(54) **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**

(71) Applicant: **Helsinn Healthcare S.A.**, Lugano/Pazzallo (CH)

(72) Inventors: **Fabio Trento**, Como (IT); **Sergio Cantoreggi**, Cagiallo (CH); **Giorgia Rossi**, Como (IT); **Roberta Cannella**, Varese (IT); **Daniele Bonadeo**, Varese (IT)

(73) Assignee: **HELSINN HEALTHCARE SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/069,927**

(22) Filed: **Nov. 1, 2013**

(65) **Prior Publication Data**

US 2014/0194395 A1 Jul. 10, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/077,462, filed on Mar. 31, 2011, now Pat. No. 8,623,826, which is a continuation of application No. PCT/IB2010/003106, filed on Nov. 18, 2010.

(60) Provisional application No. 61/262,470, filed on Nov. 18, 2009, provisional application No. 61/382,709, filed on Sep. 14, 2010.

(51) **Int. Cl.**

A61K 31/496	(2006.01)
A61K 31/573	(2006.01)
A61K 31/473	(2006.01)
A61K 9/48	(2006.01)
A61K 31/4178	(2006.01)
A61K 45/06	(2006.01)
A61K 9/20	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/496*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 9/4808*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 31/4178*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 45/06*** (2013.01); *Y10S 514/872* (2013.01)

(58) **Field of Classification Search**

USPC 514/17.7

See application file for complete search history.

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Primary Examiner — Walter Webb

(74) *Attorney, Agent, or Firm* — Troutman Sanders LLP

(57) **ABSTRACT**

Provided are compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

62 Claims, 5 Drawing Sheets

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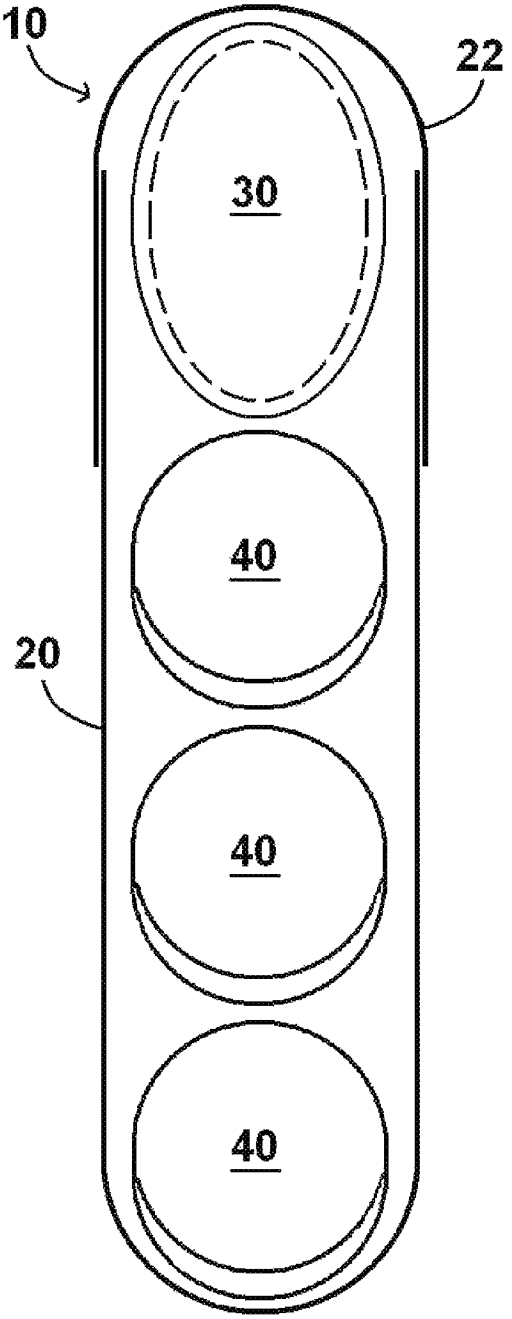


Figure 1

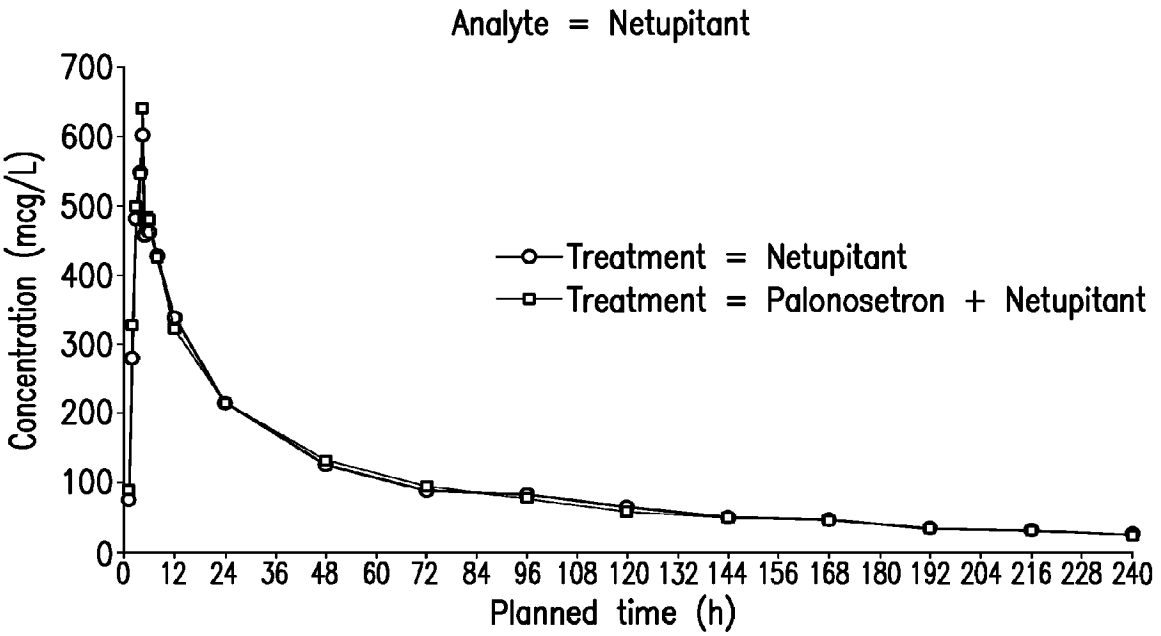

Analyte = Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment = Netupitant
Treatment = Palonosetron + Netupitant

FIG.2

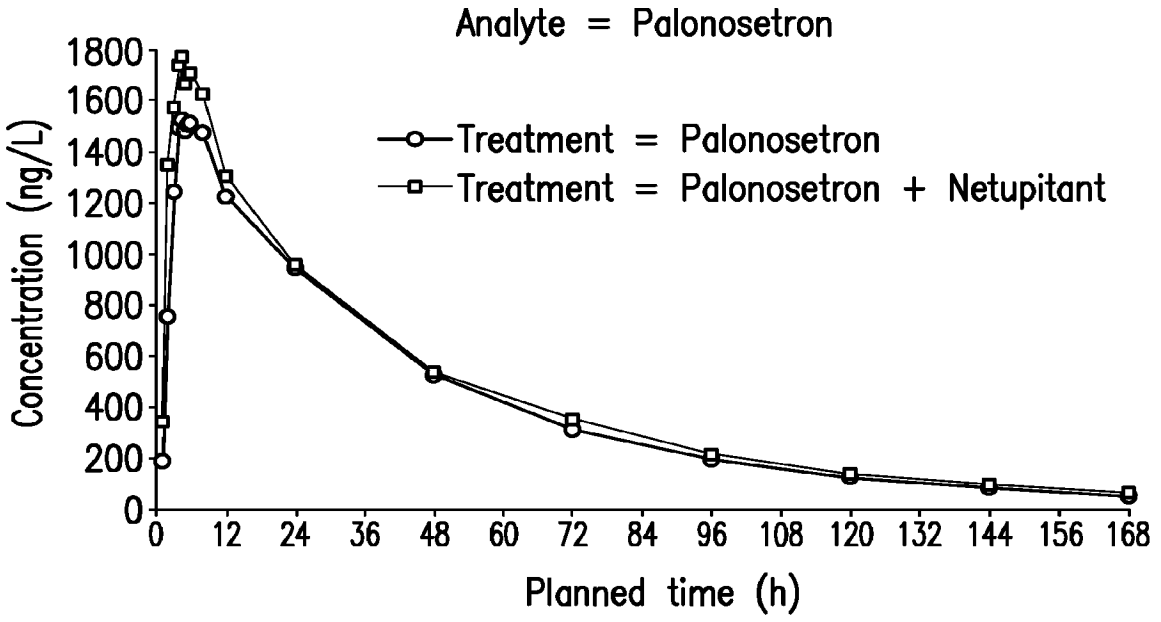

Analyte = Palonosetron
Treatment = Palonosetron
Treatment = Palonosetron + Netupitant
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)

FIG.3

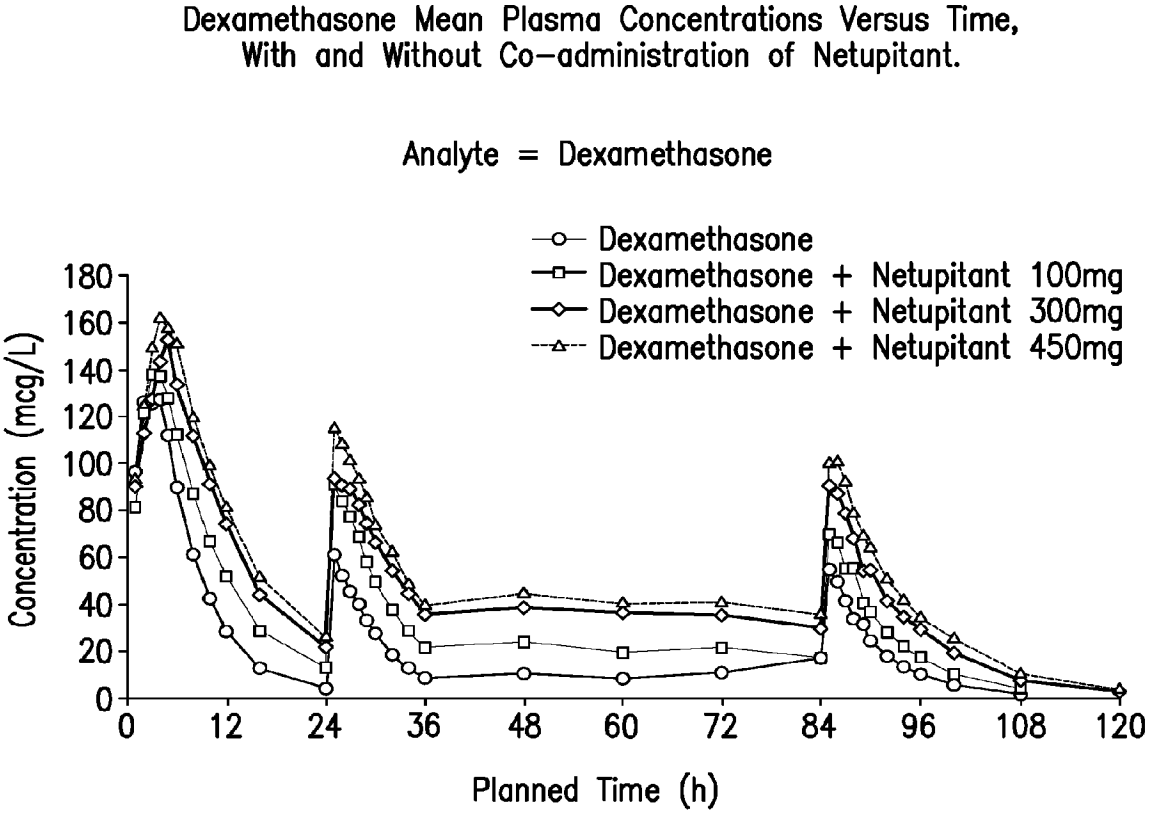

Dexamethasone Mean Plasma Concentrations Versus Time,
With and Without Co-administration of Netupitant.
Analyte = Dexamethasone
Dexamethasone
Dexamethasone + Netupitant 100mg
Dexamethasone + Netupitant 300mg
Dexamethasone + Netupitant 450mg
Concentration (mcg/L)
0
20
40
60
80
100
120
140
160
180
0
12
24
36
48
60
72
84
96
108
120
Planned Time (h)

FIG.4

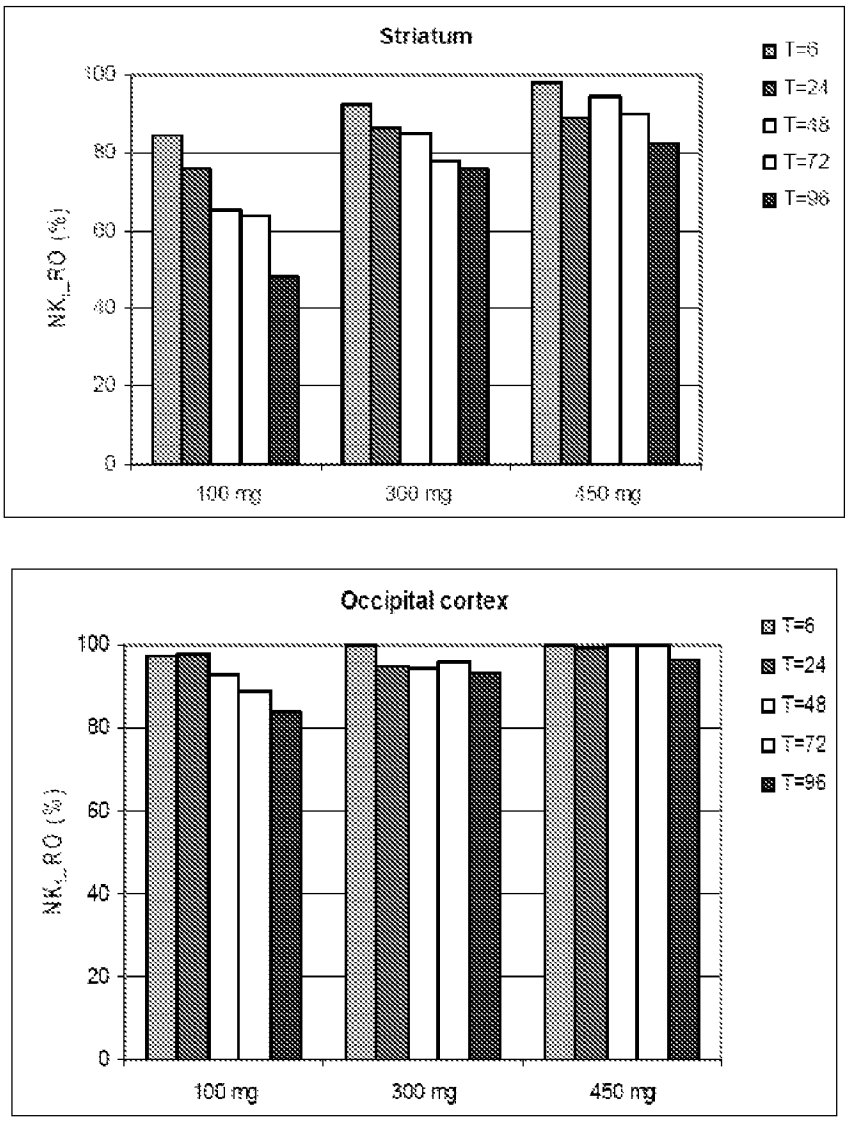

Striatum
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96
Occipital cortex
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96

FIG. 5

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/077,462, filed Mar. 31, 2011, which is a continuation of International Application No. PCT/IB2010/003106, filed Nov. 18, 2010, which claims priority to U.S. Provisional Application No. 61/262,470, filed Nov. 18, 2009, and U.S. Provisional Application No. 61/382,709, filed Sep. 14, 2010. All of the above applications are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

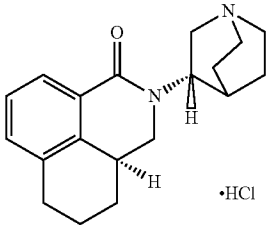
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

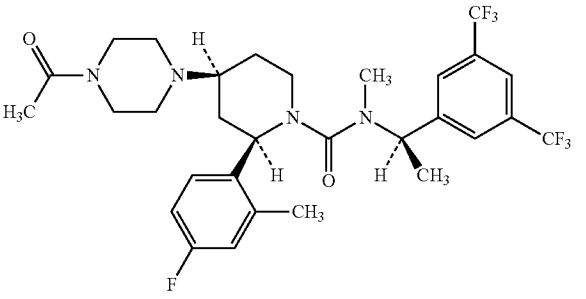
The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hberiz[de]isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O.HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:



Methods of synthesizing palonosetron are described in U.S. Pat. Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

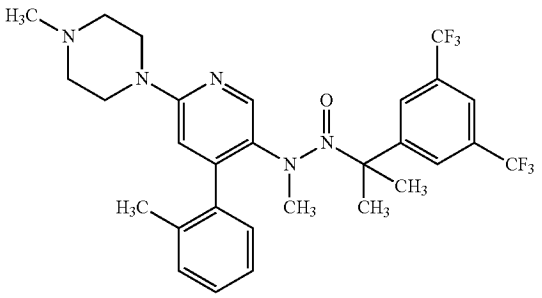
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting—not nausea—and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a 5-HT_3 antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg et al., SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp 375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition*, vol. 37, No. 8, 2009, pp. 1635-1645 to Pellegatti et al. As reported by Ruhlmann et al. in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2R,4S)-4-(4-acetylpiperazin-1-yl)-N-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-

yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Pat. Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly), FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp 1019-1045 by Huang et al.

The background of U.S. Pat. No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage

forms to reduce drug-drug interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone,

in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combination with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK_1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant—administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;
- Day 1 palonosetron—administering to said patient on day one a therapeutically effective amount of a $5\text{-}HT_3$ antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;
- Day 1 dexamethasone—administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone—when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt. %.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. **1** depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. **2** is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. **3** is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. **4** is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. **5** contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description

of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Pat. Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan et al., The Oncologist, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide>1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3 antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for

injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

FIG. **1** illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form 10 comprises a two piece hard outer shell that includes a body 20 and a cap 22. The dosage form 10 contains one palonosetron soft-gel capsule 30 (preferably containing 0.5 mg of palonosetron) and three netupitant tablets 40 (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt. % to 99 wt. %, preferably from 75 wt. % to 98 wt. %. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt. %, more preferably from 2 to 10 wt. %. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt. % to 6 wt. %, from 0.5 wt. % to 5 wt. %, or from 1.0 wt. % to 3.0 wt. %. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt. % of surfactant, and less than 10, 8, 5, 4, or even 4 wt. % of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt. % to 30 wt. % water, from 1 wt. % to 20 wt. % water, or from 2 wt. % to 10 wt. % water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt. % water, and less than 20, 15, 10, 8 or 5 wt. % water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an amount ranging from 0.01 to 10.0 wt. %, from 0.05 to 5.0 wt. %, or from 0.1 wt. % to 2.0 wt. %. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt. %.

Tablet

The tablets of the present invention can include from 20 to 95 wt. % of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt. % of netupitant. In addition, the tablets can contain diluents, disintegrants, sur-

factants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt. % of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt. % of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt. %, preferably 2 wt. %.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt. % of the tablet, and preferably 5 wt. %. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt. %. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt. % and 0.35 wt. %, respectively.

Application of the Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at room temperature, and pressure is at or near atmospheric.

Example 1

Preparation of Oral Dosage Form

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1

REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount (mg/Capsule)	Function
Fill Solution		
Palonosetron HCl	0.56[1]	Active
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	—	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	—	Shell
Sorbitol Special/Glycerin Blend 50/50	—	Plasticizer
Titanium dioxide, USP/Ph Eur	—	Colorant/Opacifier
Purified water, USP/Ph Eur	—	Solvent

[1]Corresponds to 0.50 mg. free base
[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2

REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

Example 2

Pharmacokinetics of Combined Dosage Form

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day −1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{1/2,z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as FIGS. **2** and **3**.

TABLE 3

Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h * µg/L]	22808 (7270)	22775 (10064)
AUC_{0-inf} [h * µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00; 24.00)	4.50 (3.00; 23.95)
$t_{1/2,z}$ (h)	71.81 (37.10; 261.61)	78.31 (50.17; 196.13)

Mean and SD are shown, except for t_{max} and $t_{1/2}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger C_{max}, the shorter t_{max}, (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{1/2,z}$.

TABLE 4

Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h * µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h * µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00; 8.00)	4.50 (3.00; 6.02)
$t_{1/2,z}$ (h)	34.73 (19.61; 70.46)	36.91 (20.23; 56.08)

Mean and SD are shown, except for t_{max} and $t_{1/2}$, where median and range are shown.

Example 3

Netupitant+Dexamethasone Drug Interaction Study

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (FIG. **4**). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

Example 4

Netupitant Pet Receptor Occupancy Study

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-RO_s with increasing netupitant dose. (FIG. **5**)

Example 5

Clinical Efficacy Study

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

Group 1—0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2—100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3—200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4—300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5—125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

Group 6—285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);

Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS<5 mm); No significant nausea (maximumVAS<25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.

Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);

Severity of nausea for the overall, acute and delayed phase;

• Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5

COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)
CR, Overall Phase, 0-120 h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, −24 h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120 h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively (p<0.05 for all doses).

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value, 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

Example 7

Comparative Results of Aprepitant Dosing Regimen

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Day 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 - Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[1]	89	78	<0.001
Delayed Phase[2]	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001

TABLE 8-continued

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 - Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
[1]Acute phase: 0 to 24 hours post-cisplatin treatment.
[2]Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

The invention claimed is:

1. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.

2. A method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy comprising administering to a subject receiving chemotherapy a regimen of netupitant and a sub-therapeutic dose of dexamethasone.

3. The method of claim **2**, wherein the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

4. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

5. The method of claim **1**, wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy.

6. The method of claim **1**, wherein said chemotherapy comprises carboplatin.

7. The method of claim **1**, wherein the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.

8. The method of claim **1**, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

9. The method of claim **1**, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

10. The method of claim **1**, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

11. The method of claim **2**, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

12. The method of claim **2**, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

13. The method of claim **2**, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

14. The method of claim **4**, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

15. The method of claim **4**, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

16. The method of claim **4**, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

17. The method of claim **1**, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

18. The method of claim **1**, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;

b) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

19. The method of claim **1**, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a

single administration of palonosetron or pharmaceutically acceptable salt thereof;

c) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

d) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

20. The method of claim **19**, wherein:

a) said netupitant is administered orally as the free base in a dose of from about 200 mg to about 400 mg; and

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of from about 0.25 mg to about 0.75 mg based on the weight of the free base.

21. The method of claim **19**, wherein:

a) said netupitant is administered orally as the free base in a dose of about 300 mg;

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and

c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

22. The method of claim **19**, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; and

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.

23. The method of claim **19**, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy;

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy; and

f) said dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.

24. The method of claim **19**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

25. The method of claim **19**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

26. The method of claim **19**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

27. The method of claim **19**, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

28. The method of claim **19**, wherein (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate is substantially absent from said palonosetron.

29. The method of claim **19**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

30. The method of claim **19**, wherein said chemotherapy comprises cisplatin.

31. The method of claim **19**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

32. The method of claim **19**, wherein said chemotherapy comprises cyclophosphamide.

33. The method of claim **21**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

34. The method of claim **21**, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

35. The method of claim **21**, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

36. The method of claim **21**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

37. The method of claim **21**, wherein said chemotherapy comprises cisplatin.

38. The method of claim **21**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

39. The method of claim **21**, wherein said chemotherapy comprises cyclophosphamide.

40. The method of claim **2**, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

41. The method of claim **2**, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

b) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

c) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

d) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first

dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

e) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

f) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

42. The method of claim **2**, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

c) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

d) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

e) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

f) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

g) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

43. The method of claim **35**, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy; and

c) said single administration of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant less than 2 hours prior to said chemotherapy.

44. The method of claim **35**, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy;

c) said first dose of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant, administered less than 2 hours prior to said chemotherapy; and

d) said second dose comprises about 8 mg of dexamethasone administered on days 2, 3 and 4 following said chemotherapy.

45. The method of claim **35**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

46. The method of claim **35**, wherein said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

47. The method of claim **35**, wherein said regimen is effective to prevent nausea in said patient following the administration of said chemotherapy.

48. The method of claim **35**, wherein said regimen is effective to reduce the severity of nausea in said patient following the administration of said chemotherapy.

49. The method of claim **35**, wherein said chemotherapy comprises cisplatin.

50. The method of claim **35**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

51. The method of claim **35**, wherein said chemotherapy comprises cyclophosphamide.

52. The method of claim **4**, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

53. The method of claim **4**, wherein:

a) said blood levels are induced by an intravenous antiemetic regimen administered prior to said chemotherapy; and

b) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

54. The method of claim **4**, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy

b) said blood levels are induced by an intravenous antiemetic regimen administered prior to said chemotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

55. The method of claim **54**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

56. The method of claim **54**, wherein said chemotherapy is highly emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

57. The method of claim **54**, wherein said chemotherapy is moderately emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

58. The method of claim **54**, wherein said chemotherapy is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

59. The method of claim **54**, wherein said chemotherapy is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

60. The method of claim **54**, wherein said chemotherapy comprises cisplatin.

61. The method of claim **54**, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

62. The method of claim **54**, wherein said chemotherapy comprises cyclophosphamide.

* * * * *

Exhibit D

US009403772B2

(12) **United States Patent**
Fadini et al.

(10) **Patent No.: US 9,403,772 B2**
(45) **Date of Patent: *Aug. 2, 2016**

(54) **4-(5-(2-(3,5-BIS(TRIFLUOROMETHYL) PHENYL)-N,2-DIMETHYLPROPANAMIDO)-4-(O-TOLYL)PYRIDIN-2-YL)-1-METHYL-1-((PHOSPHONOOXY)METHYL)PIPERAZIN-1-IUM AS A NEUROKININ RECEPTOR MODULATOR**

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(73) Assignee: **HELSINN HEALTHCARE SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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PCT Pub. Date: **Jun. 6, 2013**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 13/478,361, filed on May 23, 2012, now Pat. No. 8,426,450.

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**

C07D 401/04	(2006.01)
C07D 213/74	(2006.01)
C07D 213/89	(2006.01)
C07F 9/06	(2006.01)
C07D 213/72	(2006.01)
C07D 213/76	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 213/89*** (2013.01); ***C07D 213/72*** (2013.01); ***C07D 213/74*** (2013.01); ***C07D 213/76*** (2013.01); ***C07D 401/04*** (2013.01); ***C07F 9/062*** (2013.01)

(58) **Field of Classification Search**

CPC C07D 213/74; C07D 401/04
USPC 544/360; 546/304
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Douglas M Willis
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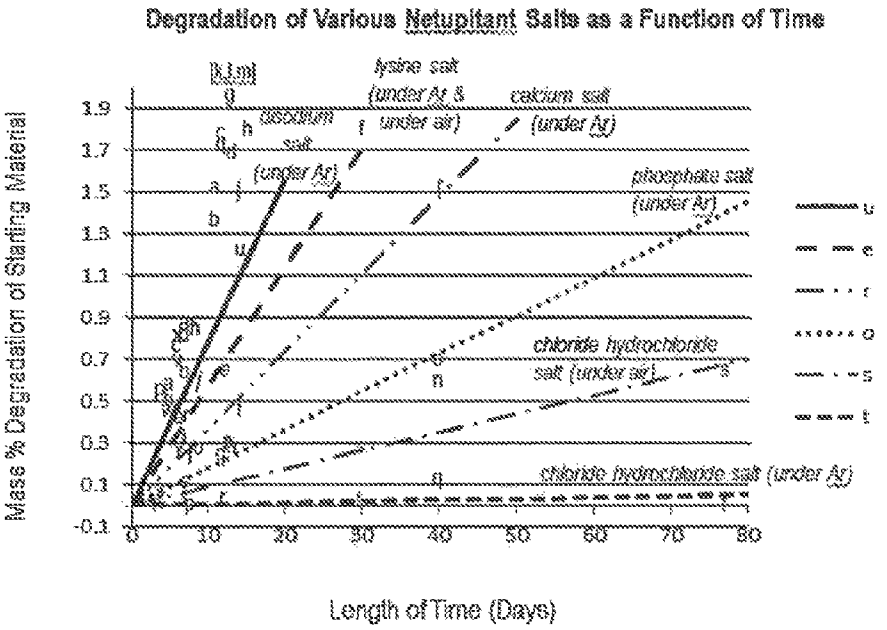
(57) **ABSTRACT**

Compounds and methods for the prevention and/or treatment of diseases which are pathophysiologically mediated by the neurokinin (NK_1) receptor, based on 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl) 3yridine-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium and pharmaceutically acceptable salts thereof.

14 Claims, 1 Drawing Sheet



Degradation Behavior Over Time for Various Salts of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phos-phonooxy)methyl)piperazin-1-ium.

4-(5-(2-(3,5-BIS(TRIFLUOROMETHYL) PHENYL)-N,2-DIMETHYLPROPANAMIDO)-4-(O-TOLYL)PYRIDIN-2-YL)-1-METHYL-1-((PHOSPHONOOXY)METHYL)PIPERAZIN-1-IUM AS A NEUROKININ RECEPTOR MODULATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 61/564,537, filed Nov. 29, 2011, and is a continuation in part of U.S. Non-provisional application Ser. No. 13/478,361, filed May 23, 2012.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

2. Description of Related Art

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et al. (*Science* 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis. Gesztesi et al. (*Anesthesiology* 93(4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis

U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron (a $5\text{-}HT_3$ receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-oxide derivatives are reported in the '026 patent.

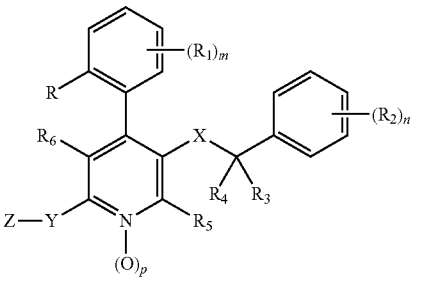
U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclose how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as prodrug structure(s), prodrug stability, synthetic cost, and selectivity of the phosphoryloxymethylation protocol.

In view of the above, there is a need to find new derivatives of and methods for making 4-phenyl-pyridine compounds that are effective NK1 receptor antagonists, and that have enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives that are particularly well-suited for antagonizing the NK_1 receptor and that have the following general formula (I):

Formula (I)



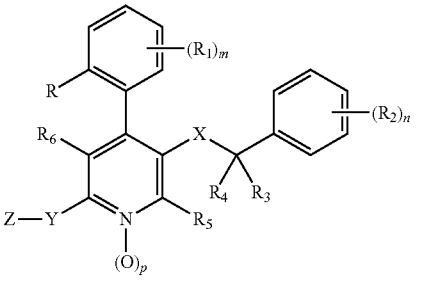
and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

In one embodiment the invention is a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof,

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

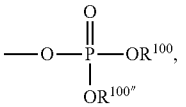
X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101} alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

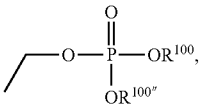
Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101} alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:

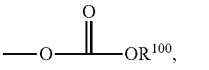
(Ia)

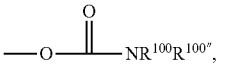
(Ib)

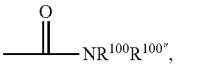
(Ic)


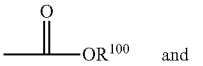
(Id)


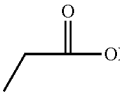
-continued

(Ie)


(If)


(Ig)


(Ih)

and

(Ii)


where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{10}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

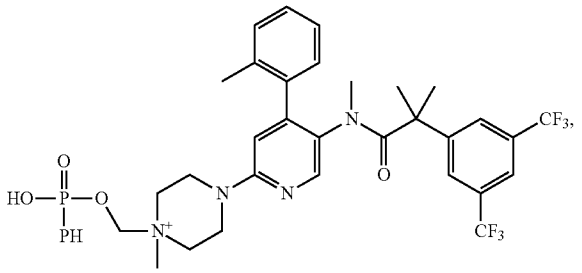
with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one.

In another embodiment the invention is the use of a therapeutically effective amount of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or adduct thereof, in the manufacture of a medicament which is able to treat emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof.

In an alternative embodiment the invention is a method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) as defined above.

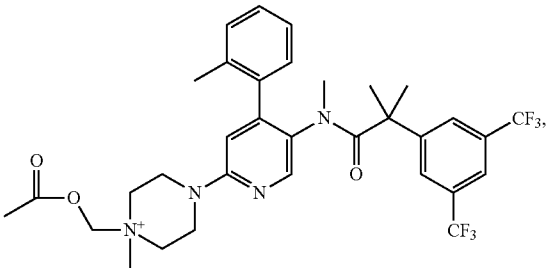
In still another embodiment the invention is a compound selected from the group consisting of:

GA1



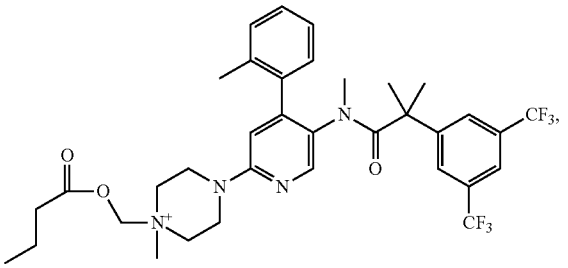
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium

GA2



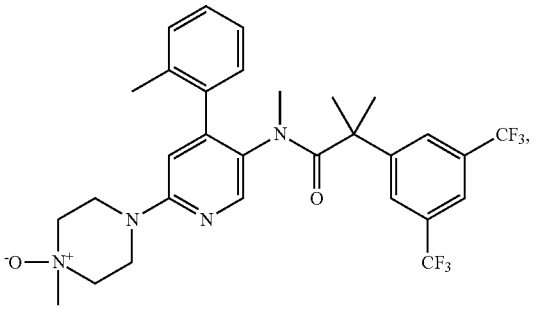
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium

GA3



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl-1-methylpiperazin-1-ium

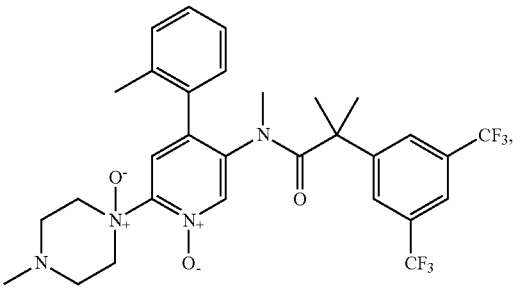
GA4



1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

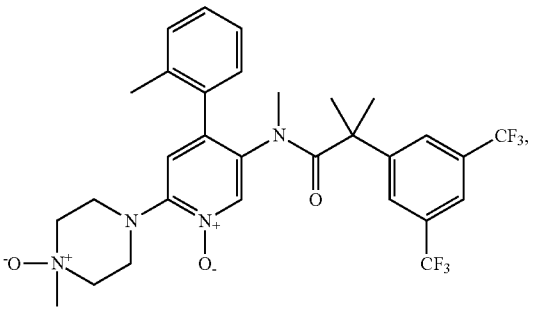
-continued

GA5



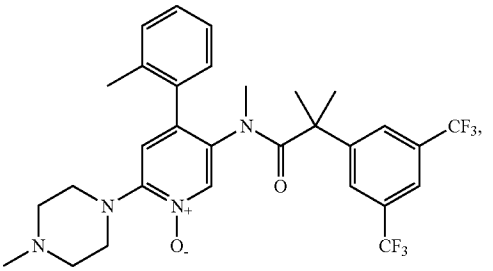
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine-1-oxide

GA6



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine-1-oxide

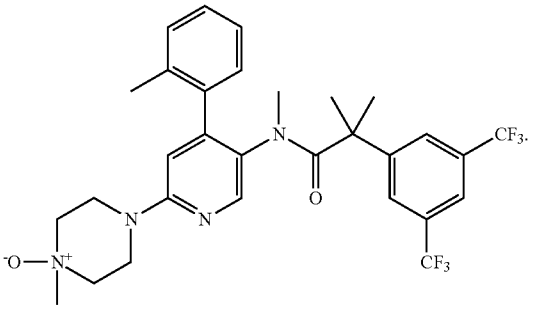
GA7



5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

and

GA8

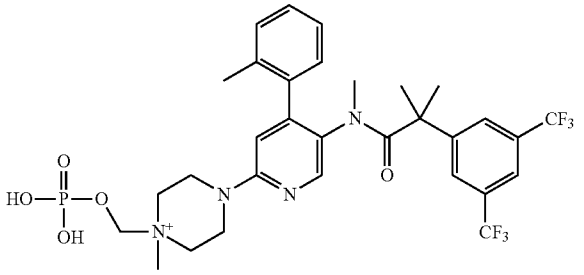


4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine-1-oxide

or a pharmaceutically acceptable salt or adduct thereof.

In a further embodiment the invention is a compound of formula GA1,

formula GA1



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazine-1-ium

or a pharmaceutically acceptable salt or adduct thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** reproduces stability data for various salts of 4-(5-(2-(3,5-bis(trifluoro-methyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphornooxy)methyl)piperazin-1-ium.

DETAILED DESCRIPTION

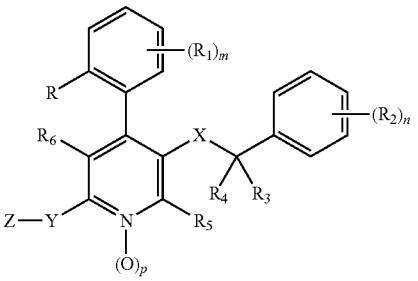
Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

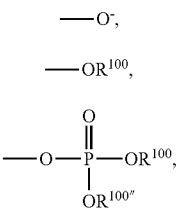
R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101} alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:



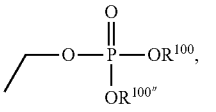
(Ia)

(Ib)

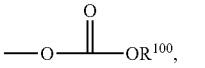
(Ic)

-continued

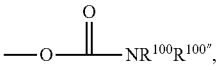
(Id)



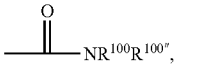
(Ie)



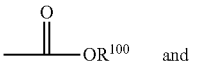
(If)



(Ig)

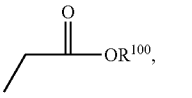


(Ih)



and

(Ii)



where formula (Ia) refers to an oxide;

R^{101}, R^{101}", R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, R^{100}", together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

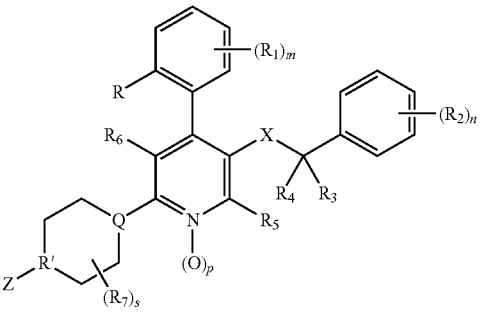
R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is from 0 to 4; n is from 0 to 5; p is from 0 to 1; and with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein X is —$NR^{101}C(O)$. In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

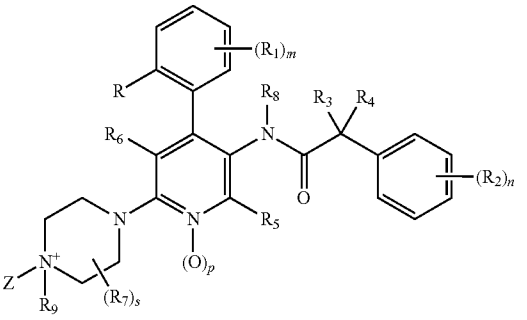
Formula (II)



where Q and R' are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

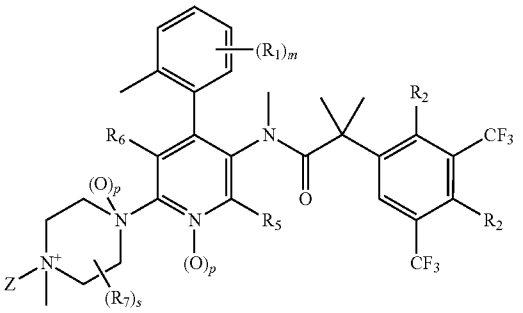
Formula (III)



where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

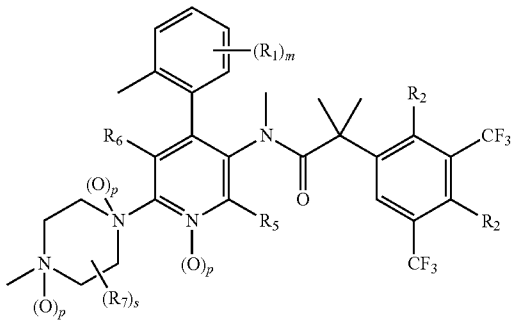
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

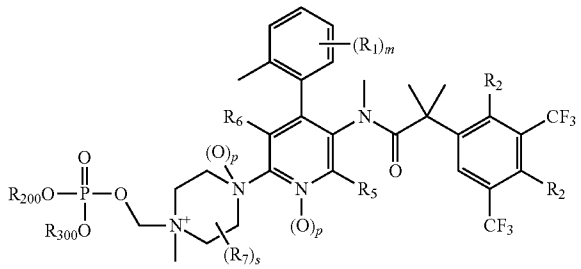
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (VI):

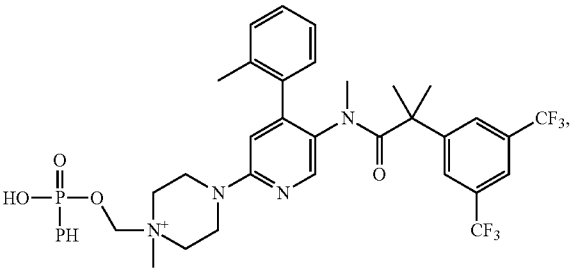
Formula (VI)



where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

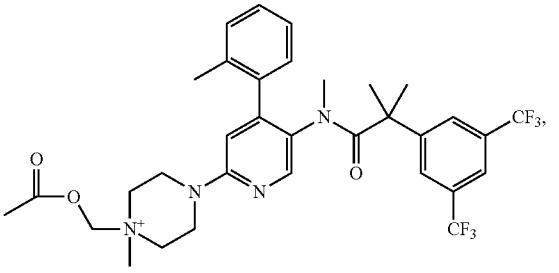
In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of:

GA1



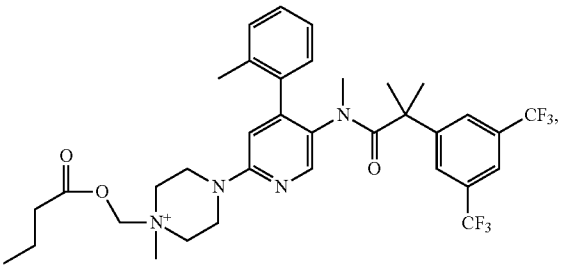
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium

GA2



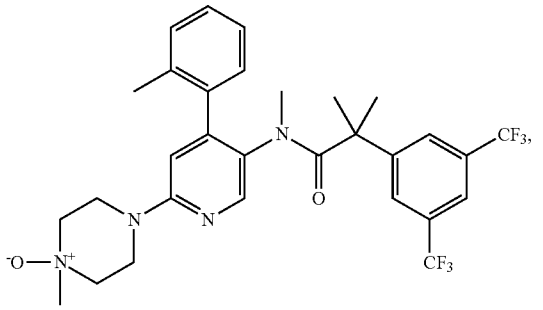
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium

GA3



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl-1-methylpiperazin-1-ium

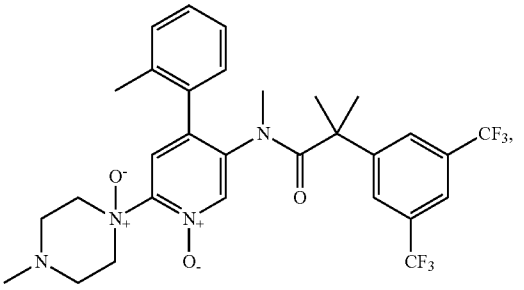
GA4



1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

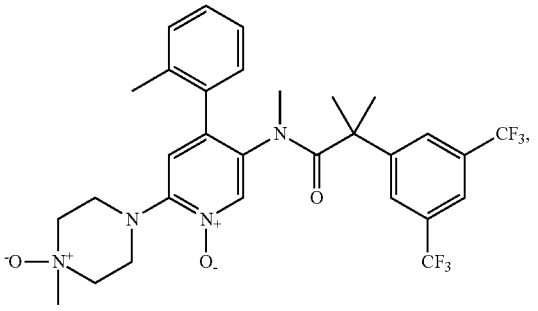
-continued

GA5



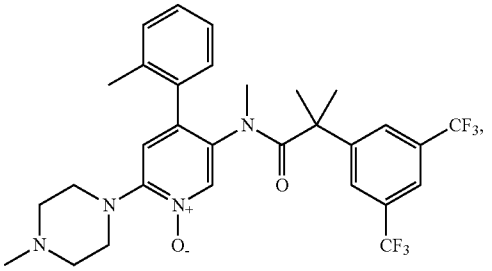
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine-1-oxide

GA6



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine-1-oxide

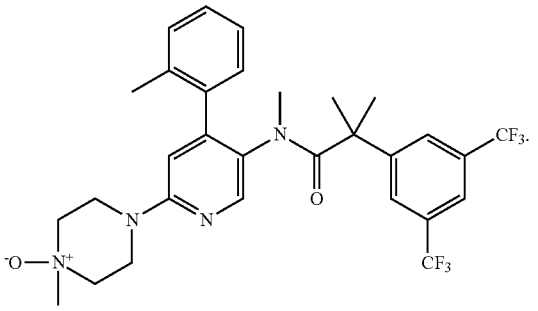
GA7



and

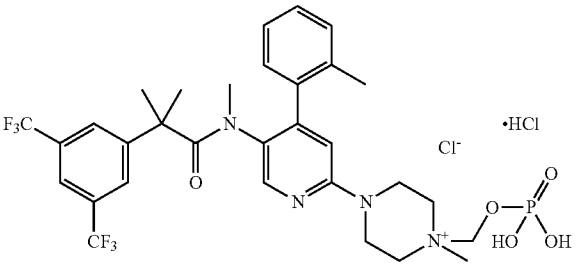
5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

GA8



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine-1-oxide

A particular preferred compound is the chloride hydrochloride HCl salt of GA1 having the following chemical structure which, it has been found, is tremendously resistant to decoupling of the oxo-phosphonomethyl, and reversion of the active moiety to its parent state.



Salts and Adducts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced storage stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

The disclosed compositions and compounds can be used in the form of adducts derived by formation of Lewis pairs, covalently linked adducts e.g. between N atoms and carbonyl-containing reactants, hydrates and alcoholates, host-guest adducts containing molecular species not bonded or associated with the medicinal compound, and other clathrates.

Depending on the particular compound, an adduct of the compound can be advantageous due to one or more of the adduct's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, an adduct of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where an adduct is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the adduct preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable adduct" refers to an adduct prepared by combining a compound, such as the disclosed compounds, with a gas, water, solvent, Lewis base, carbonyl-containing molecule, or guest molecule that is generally considered suitable for human consumption. Pharmaceutically acceptable addition species are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the adducts of the disclosed compounds are non-toxic "pharmaceutically acceptable adducts." Adducts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic adducts of the disclosed compounds which are generally prepared by reacting a compound of the invention with a suitable organic or inorganic addition species.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, include those derived from Lewis bases such as boric acid, aluminum hydroxide, organic sulfoxides, organic sulfones, organic sulfonium salts, H_3PO_3, siloxanes, and other Lewis bases.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from covalent bonding between an oxygen, nitrogen or sulfur atom of the compound and carbon dioxide, low alkyl aldehyde or ketone, vanillin, amino acid, or a nucleic acid.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from inclusion of an unbonded gas such as dioxygen, dinitrogen, carbon dioxide, nitrous oxide, ethyl ether, or other gas, contained within but not bonded to a crystalline or amorphous phase of the compound.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from association of a molecule of the compound with water, a pharmaceutically acceptable lower alkyl alcohol, or another pharmaceutically acceptable solvent that is associated in a molecular ratio with the compound.

In one embodiment the adduct is optionally a clathrate.

General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W.

Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

The invention further provides methods for making suitable prodrugs of the 4-phenyl-pyridine derivatives. In one embodiment the invention provides a one-step, acid-free synthesis for functionalizing tertiary amines by reaction with chloromethyl dialkyl phosphate esters to create (phosphooxy)methyl prodrugs that are substrates for phosphatase enzymes. By contrast the prior art had required multiple synthetic steps for comparable reactions, including requiring the use of proton scavengers during initial reaction and requiring strong acid to deprotect the phosphate group in another step. In another embodiment the invention provides methods for making chloromethyl dialkyl phosphate esters having suitable purity and economy, because the quality of phosphate ester compositions from commercial sources is too low to provide acceptable yields for reactions according to the invention. In an additional embodiment the invention provides a method to stabilize the (phosphooxy)methyl prodrugs according to the invention by combination with two equivalents of hydrochloric acid, because whereas the prior art preferred the use of dibasic salts of (phosphooxy)methyl substituents for quaternary ammonium salts in prodrugs, the

present invention had found that such salts are unstable and reform the underlying drug during storage.

DEFINITION OF TERMS

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms. In one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y—," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X-Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile") —CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The term "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substitu-

ents include monoalkylamino such as methylamino (exemplified by the formula —NH(CH_3)), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to =O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkcylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to =S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxido" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane, thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or

"pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2—. The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2—. The term "methylenoxy" refers to the group —CH_2—O—. The term "methylenethioxy" refers to the group —CH_2—S—. The term "methylenamino" refers to the group —CH_2—N(H)—. The term "ethylenoxy" refers to the group —CH_2—CH_2—O—. The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule. If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active compounds and compositions, for example, can be administered orally, rectally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile

injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

In some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide$\geq$1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant

derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg. orally on day 1, followed by 8 mg. orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously administered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-day course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said 5-HT_3 antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg, or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 mL.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodiment, the netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease. In some other forms, disclosed

are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

More Definitions of Terms

1. A, an, the

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes not only single carriers but also mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. In order to more fully document the state of the art to which this invention pertains, the disclosures of these publications are to be considered as being referenced individually, specifically and in their entireties for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

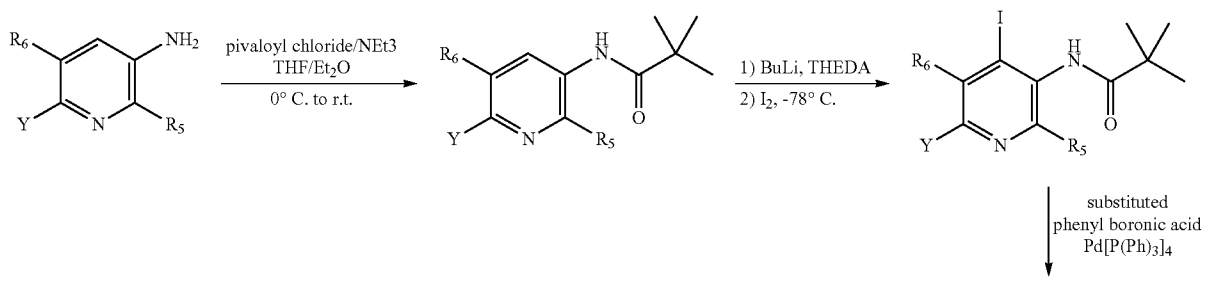
Example 1

Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

General Scheme of Preparing Compounds of Formula (I)

Scheme 1



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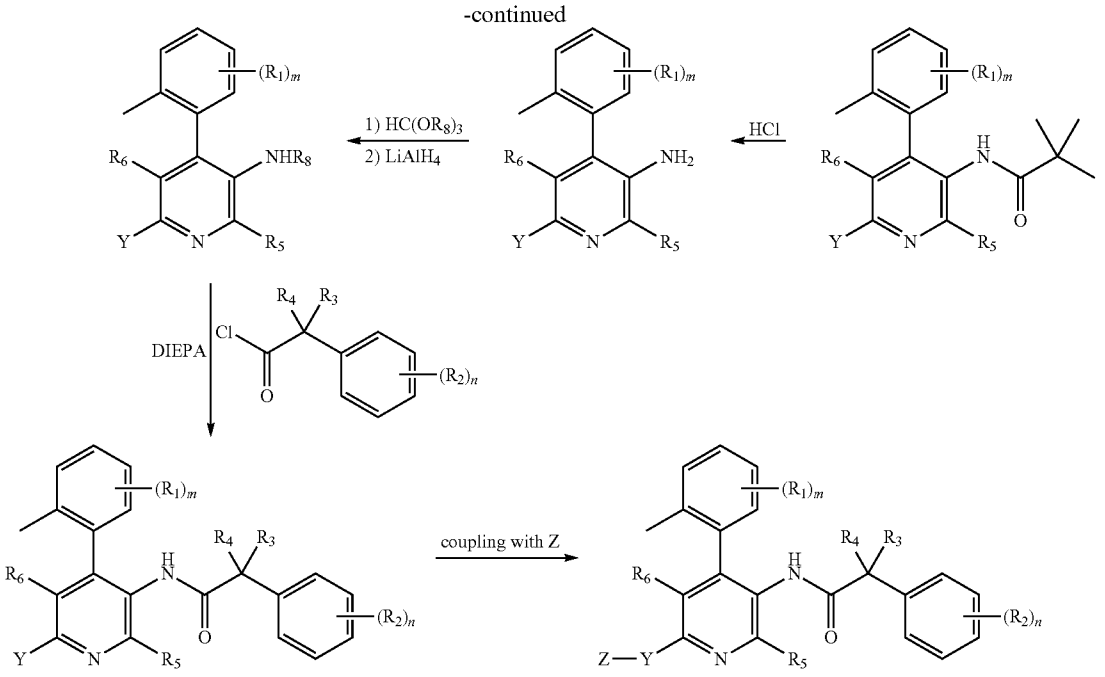
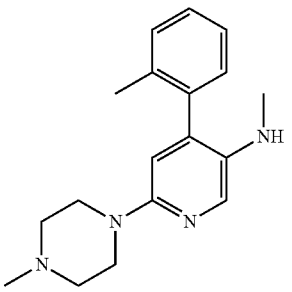


Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, which are referenced individually, specifically and in their entireties for the material contained in them that is relevant to the preparation of intermediate I.

Synthesis of methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THF were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolylmagnesium chloride solution (1M in THF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THF removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent: ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution. The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THF were added 3.1 ml (42.0 mMol) thionylchloride and 143 .mu.l (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0° C. After 30 minutes at 0° C., THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as a beige crystalline foam. MS (ISP): 247 ($M+H^+$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamide in 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam.

MS (ISP): 311 ($M+H^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol

4:1) to yield 100 mg (70%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 ($M+H^+$, 100), 226 (42).

Step 5:

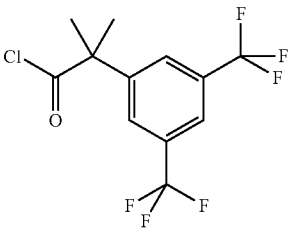
2.15 mil (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH=8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam.

MS (ISP): 341 ($M+H^+$, 100), 284 (35).

Step 6:

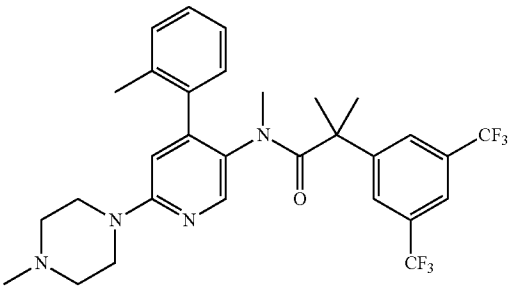
A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-Al® (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 ($M+H^+$, 100).

Synthesis of 2-(3,5-bis-Trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution was rotary evaporated to dryness. 9 ml Toluene were added and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, $3H_{arom}$); 1.77 (s, 6H, 2 CH_3).

Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)

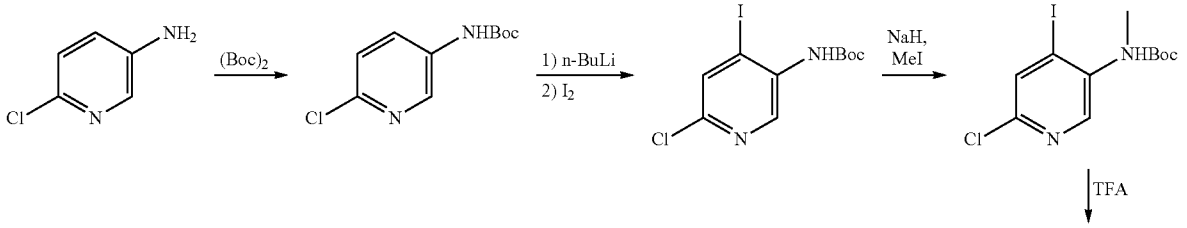


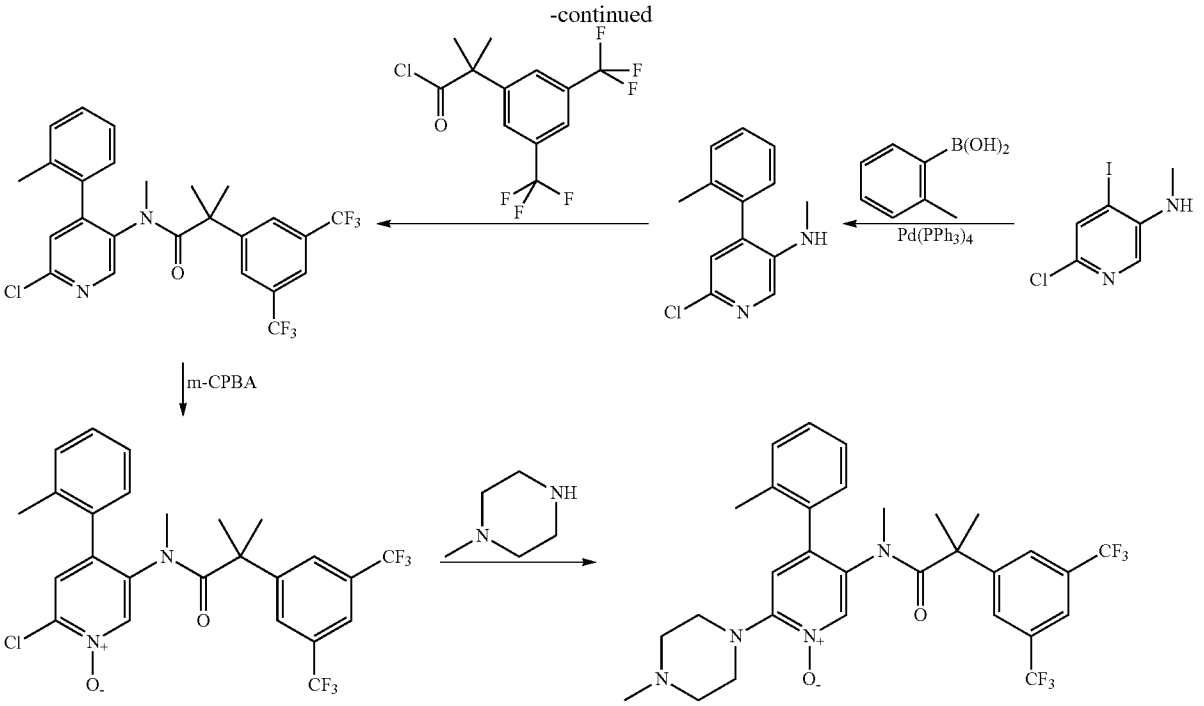
A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol)$_2$-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide as white crystals.

M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2





Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl(6-chloropyridin-3-yl)carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl(6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THF was added n-BuLi (600 mL, 1.5 mol) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THF was added. Then the solution was stirred at −78° C. for 4 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl(6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl(6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 mL of anhydrous THF was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THF was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl(6-chloro-4-iodopyridin-3-yl)(methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl(6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 mL of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol). The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under N_2 atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature.

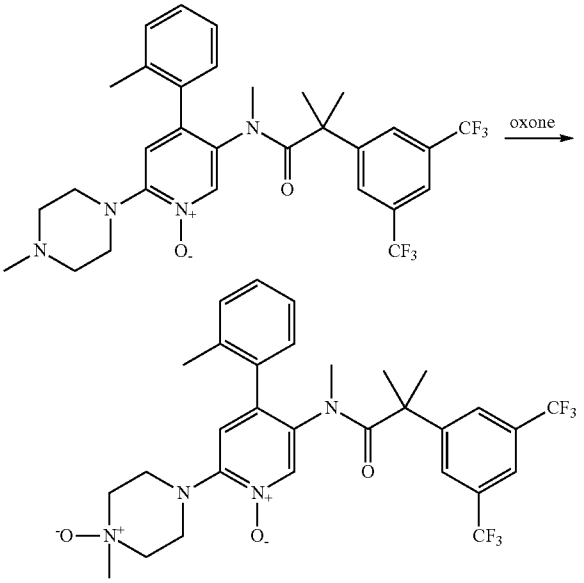
1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45~1.20 (m, 6H).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide

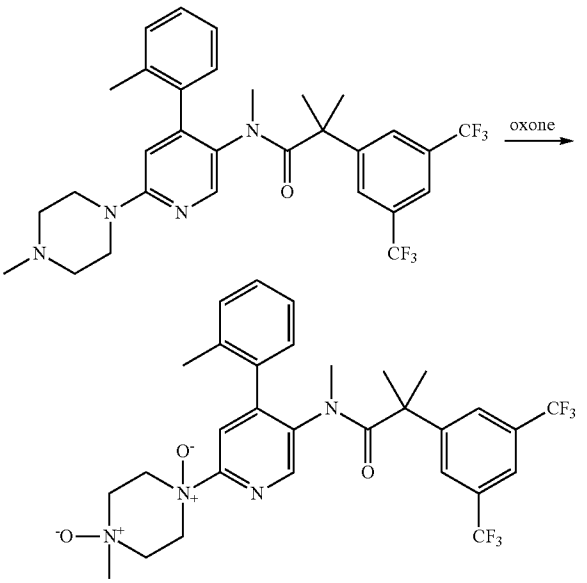
Scheme 3



To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 mL of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for 4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37~7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 21H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

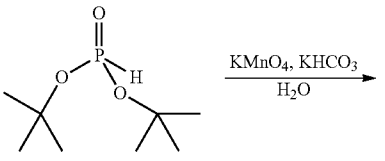
Scheme 4



To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (3.38 g, 40.3 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR (CDCl3, 400 MHz, at 333K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26~7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

Synthesis (A) of di-tert-butyl(chloromethyl)phosphate

Scheme 5



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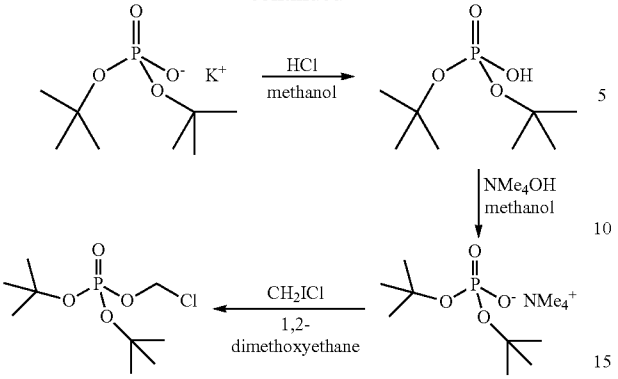
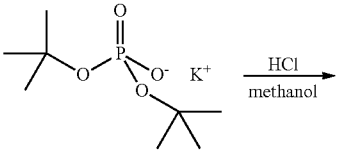


Di-tert-butyl phosphohite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time. The reaction as then allowed to continue at room temperature for an additional half hour.

Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the crude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloroiodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis (trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium without further purifications (60% yield): ^{1H}NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Synthesis (B) of
di-tert-butyl(chloromethyl)phosphate

Scheme 5A



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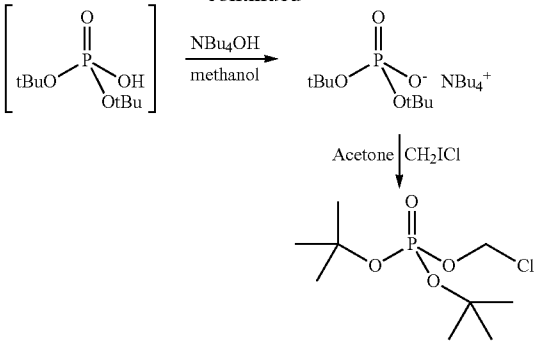
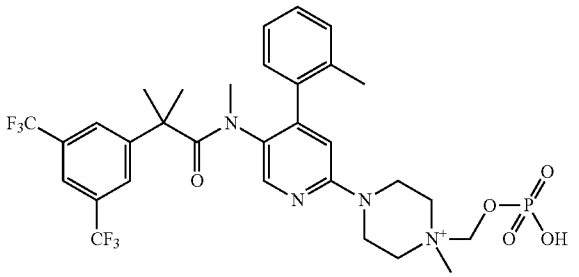


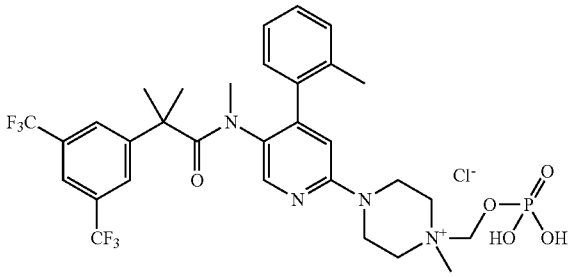
Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) is dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetrabuthylammonium hydroxide 1 M in methanol (20.14 mmole) while keeping the reaction cooled at 0° C. with efficient stirring. The resulting clear solution is placed under reduced pressure to give the intermediate product. The tetrabuthylammonium di-tert-butyl-phosphate dissolved in acetone is then added dropwise to 53.3 grams of chloroiodomethane (302.1 mmole) and stirred at 40° C. for 1-2 hours. The solvent and excess of chloroiodomethane are distilled off, the reaction mass suspended in TBME and then filtered. The filtrate is washed by a saturated solution of sodium bicarbonate and water and then placed under reduced pressure to substitute the solvent by acetone, i.e., to remove the solvent after which it is replaced with acetone. The chloromethyl di-tert-butyl phosphate 7-20% in acetone is used in the next step without further purifications (70-80% yield): ^{1}H-NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Stability studies of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium salts

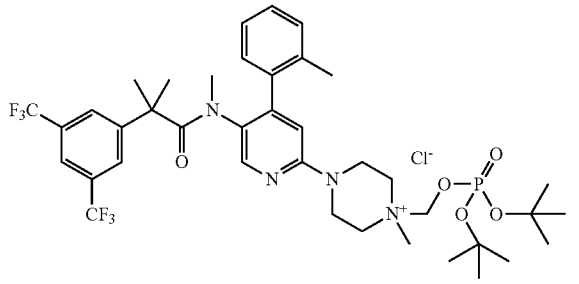
In order to further improve the stability and solubility of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium, a variety of its derivative salts were synthesized and tested. Their synthesis employed either a) neutralization of the dried diacid phosphate species and its corresponding base salts or b) a direct acid deprotection starting from the dried di(tert-butyl)-protected phosphate species. Neutralization was performed with L-histidine, magnesium salt, N-methyl-D-glucamine (dimeglumine), and L-lysine. Both procedures were tried in the synthesis of citric derivatives whereas with other acids the direct deprotection reaction was used. The figures below show the most relevant structures.



Parent acid species

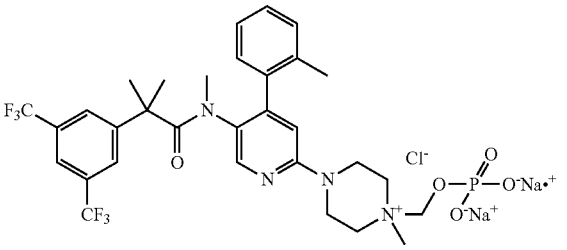


Diacid phosphate species

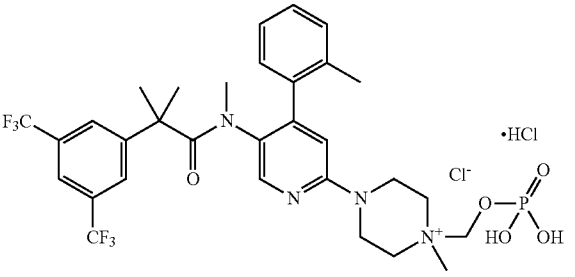


Protected phosphate species

-continued



Dibasic phosphate species



Chloride hydrochloride species

When the parent acid species was not stored in dry condition it was found to undergo over 8% degradation in the first week and over 65% degradation in the first six months. When the dried parent acid species was held at 30° C. in air it underwent 0.05% degradation in the first 7 days and at total of 7.03% degradation in six months. When the dried parent acid species was held under argon at room temperature it underwent up to 0.13% degradation in the first 7 days but then was essentially stable for six months. Results for various derivative salts are shown in Table 1 below.

TABLE 1

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	L-Histidine, 2 eq.	26.6%	95.94%	Degradation: +0.70% in 6 days (in air) +0.46% in 6 days (in argon)
MeOH	$Mg(OH)_2$, 2 eq.	48.6%	94.11%	Degradation: +0.81% in 6 days (in air) +0.29% in 6 days (in argon)
MeOH + DCM, 1:1	Citric acid, 2 eq.	N.A.	94.40%	From protected species.
MeOH	1. HCl dioxane, 4 eq. 2. $Ca(OH)_2$	>90%	94.50%	From protected species.
MeOH	H_3PO_4, 85%, 2 eq.	>90%	98.81%	From protected species and retains 0.39% of that species.
MeOH	HBr, 48%, 4 eq.	84.6%	96.11%	From protected species. Product degrades rapidly,
MeOH + DCM, 1:4	CH_3SO_3H	N.A.	61.54%	From protected species. Product NOT stable: contains 32.45% decomposition species.
MeOH	NaH_2PO_4, 4 eq.	N.A.	n.d.	Only 1.27 of parent species formed. Poor reaction.
MeOH	N-methyl-D-glucamine (Meglumine), 2 eq.	N.A.	96.88%	Degradation: +0.87% in 6 days (in air) +1.52% in 11 days (in argon)
MeOH	N-methyl-D-glucamine (Meglumine), 1 eq.	>99%	97.42%	Degradation: +0.77% in 6 days (in air) +0.83% in 7 days (in argon)

TABLE 1-continued

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH+ DCM, 5:2	1. NaOH, 3 eq 2. Citric acid, 1 eq.	96.5%	97.49%	Degradation: +0.09% in 2 days (in argon) +0.59% in 89 days (in argon)
MeOH+ DCM, 5:2	1. NaOH, 3 eq. 2. Fumaric acid, 1 eq.	93.8%	97.46%	Degradation: +1.95% in 14 days (in air) +1.80% in 12 days (in argon)
MeOH	L-lysine, 1 eq.	>99%	97.62%	Degradation: +0.69% in 14 days (in air) +0.48% in 12 days (in argon)

A more comprehensive showing of stability results is given in FIG. **1**, where the horizontal axis represents number of days of testing and the vertical axis represents the mass percent of degradation. Alphabetical letters are used to denote data points on the graph that correspond to degradation percentage values over time for respective salts of the same parent compound as just described above and in Table 2 below. The drawn lines correspond to general trends over periods of days for the benchmark salt (the disodium salt) and for the few salts that manifested more desirable results than the disodium salt.

TABLE 2

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
a	2 Dimeglumine	Air
b	2 Dimeglumine	Argon
c	Dimeglumine	Air
d	Dimeglumine	Argon
e	Lysine	Air
f	Lysine	Argon
g	Fumarate	Air
h	Fumarate	Argon
i	Citrate	Air

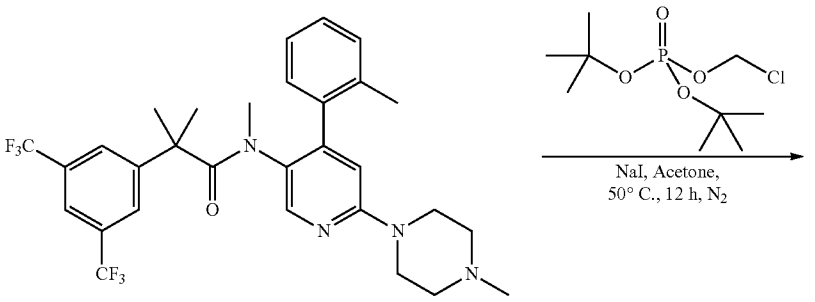
TABLE 2-continued

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
j	Citrate	Argon
k	Bromide	Air
l	Bromide	Argon
m	Mesylate	Nitrogen
n	Phosphate	Air
o	Phosphate	Argon
p	Citrate	Nitrogen
q	Calcium	Air
r	Calcium	Argon
s	Chloride hydrochloride, anhydrous	Air
t	Chloride hydrochloride, anhydrous	Argon
u	Disodium Salt	Air
v	Histidine	Air
w	Histidine	Argon
x	Magnesium	Air
y	Magnesium	Argon

Synthesis (A) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

Scheme 6



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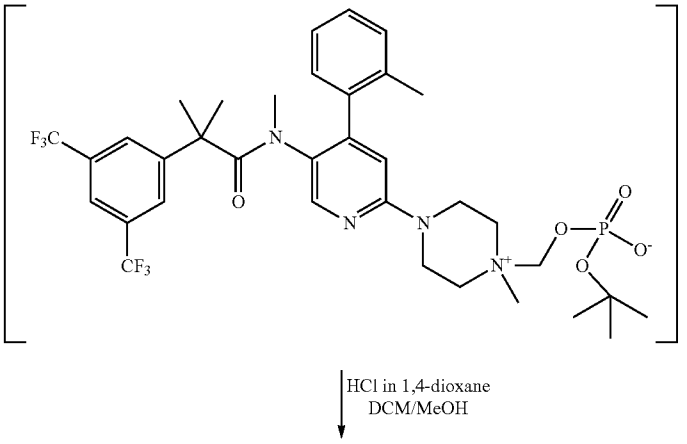
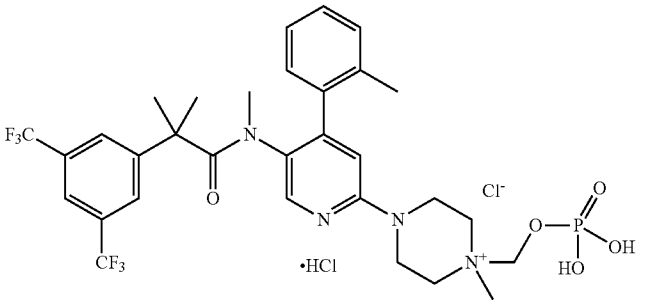




The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile. 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphtalene and 46.6 g (80.54 mmole) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropylether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropylether/acetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-7.10 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m. 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride as white solid (Yield: 88-93%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

Synthesis (B) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

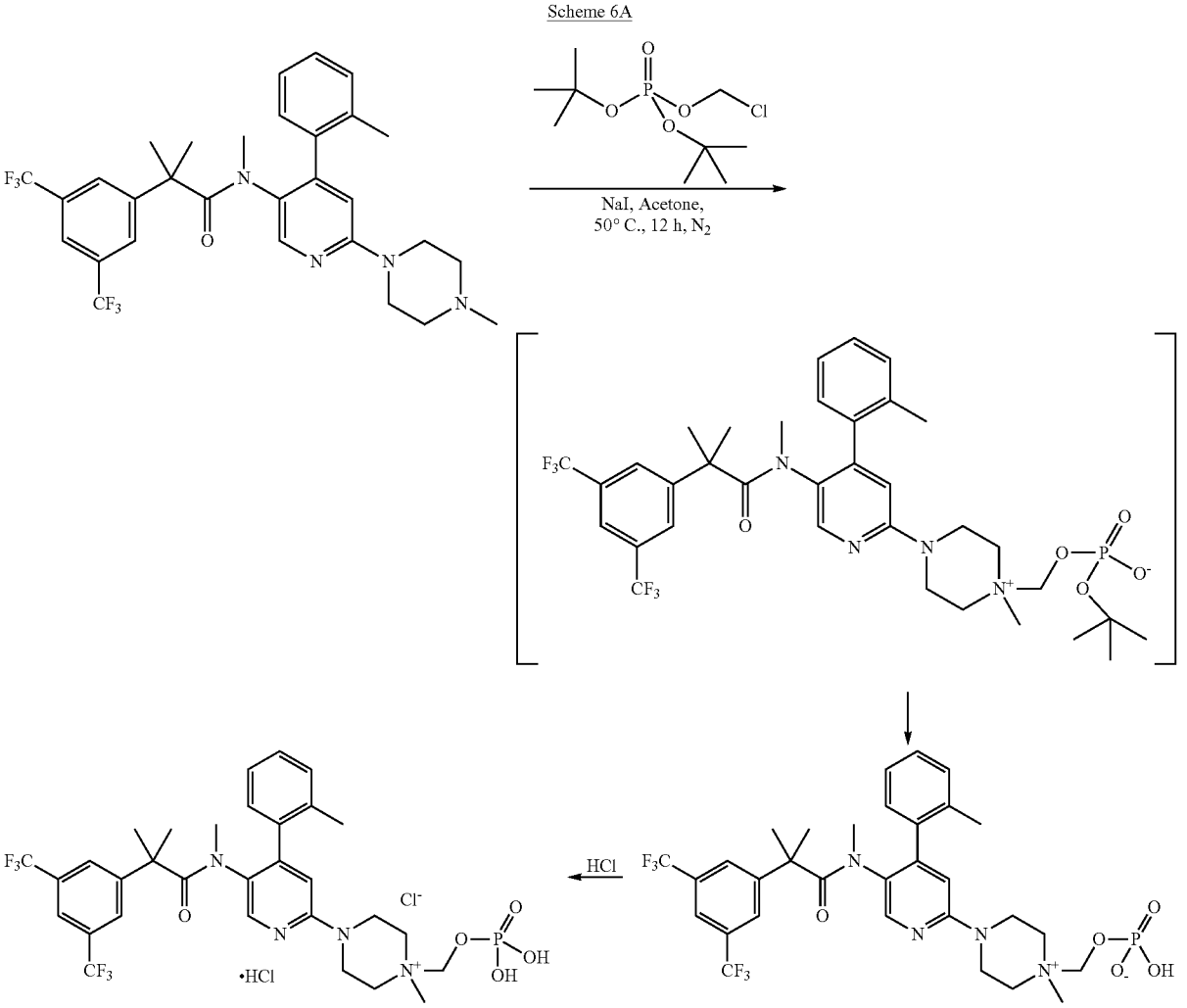
To the solution of chloromethyl di-tert-butyl phosphate in Acetone (22.1 g from a 10% solution, 85.58 mmole), 15.5 g (103.24 mmole) of sodium iodide and 33.0 g (57.00 mmole) of netupitant were added and the solution heated at 50° C. for at 6-16 h. The precipitated salts were filtered off, the acetone distilled under reduced pressure and the crude product dissolved in 43.0 g of methanol and 43.0 g 1,4-dioxane. 12.6 g of HCl 4M in dioxane (113.85 mmole) were added, and then methanol is distilled off at 40° C. under reduced pressure. The solution is cooled at 5° C. and stirred at 5° C. for at least 2 h at 5° C. The product was isolated by filtration, purified by additional slurry in acetone (238 g), and filtered and washed with acetone (47 g) and pentane (2×72 g).

The product was finally dried under reduced pressure at 60° C. to afford 22-30 g of white-yellowish solid (Yield: 50-70%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

It is to be understood that the product shown in Scheme 6. A is illustrative, being just one of several permutations in which the acidic protons bond to various atoms in an equilibrium. For instance depiction of other permutations would show a proton bound to one or more of the N atoms while one or more of the O atoms bound to the P atom would bear an anionic charge. The invention comprises all of the molecular species within that equilibrium and the product shown in the FIGURE is intended to represent all of them in a generic fashion.

Scheme 6A



7. Evaluation of Representative Compounds of Formula (I)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 3 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE 3

Chemical Stability and Solubility of Representative Compounds

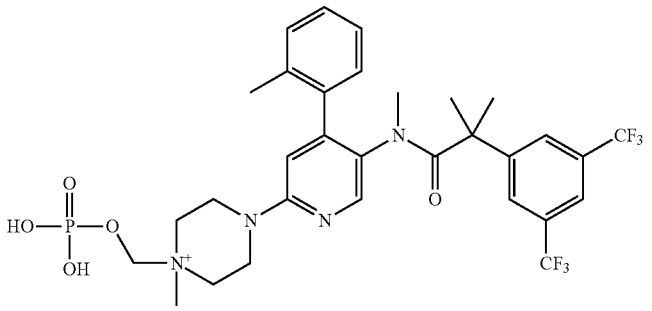
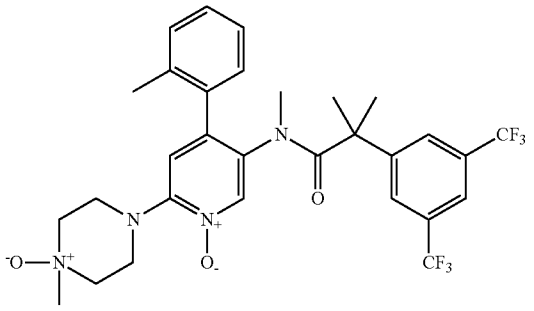
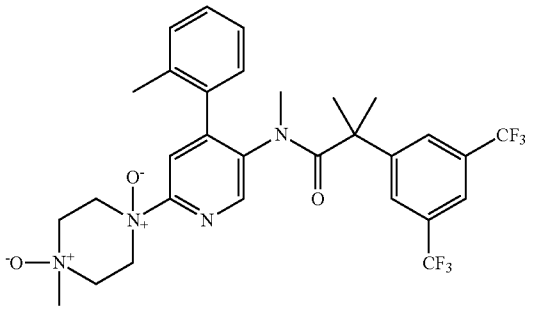
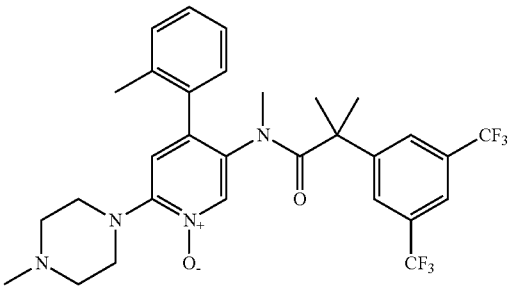
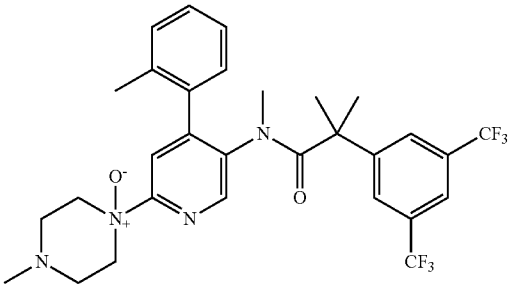
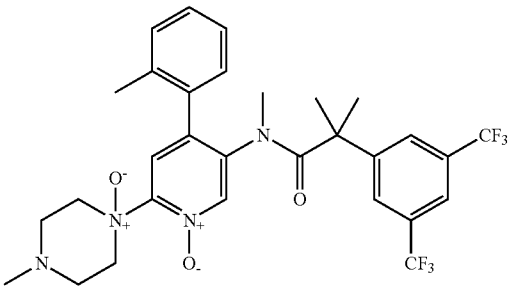
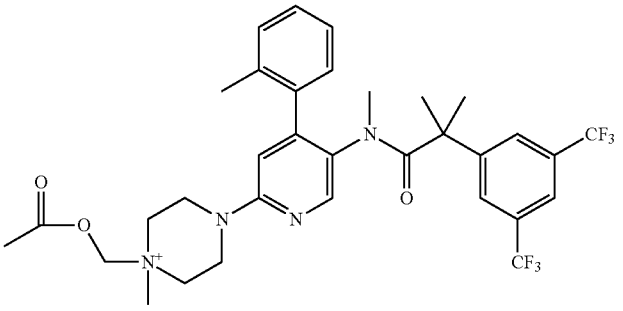
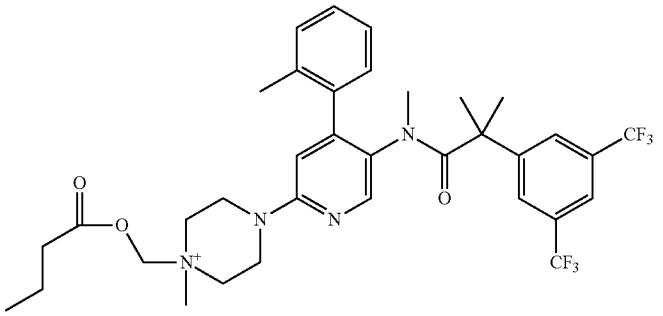
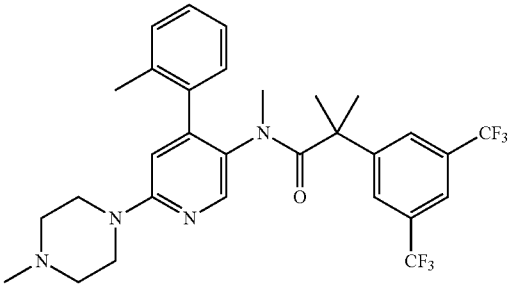
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1		medium	10-15 mg/ml
2		high	>10 mg/ml
3		high	>10 mg/ml
4		medium	~0.6 mg/ml
5*		medium	~1 mg/ml

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
6		low	N/A
7		low	insoluble
8		Low	insoluble
9*			0.25

*Reference Compound

ii. Local Tolerance

In contrast to netupitant (compound no. 9 in the above table), seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

There were minimal signs of inflammation at injection site and there was little edema;

No later stage thrombus was found in any animal studied;

Severity of inflammation was similar in compound and vehicle-treated animals;

No tissue necrosis was observed in any of the tails; and

The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 3), as compared to a reference compound—netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow

bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a dose volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Before administration, rats were fasted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pre-dose and at 0.05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO:Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solubility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (TV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC. MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 3, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 4:

TABLE 4

Comparative Bioequivalence Studies of Netupitant and Related Compounds

	IV			PO
	Compound 1	Compound 2	Compound 3	Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng · min/ml)	315627	88732	192730	307285
Bioequivalence (%)	103	29	63	

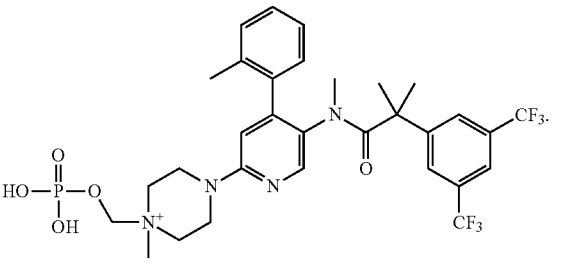
*Reference Compound

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby referenced individually and specifically for the material contained in them that is discussed in the sentence in which the reference is relied upon. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

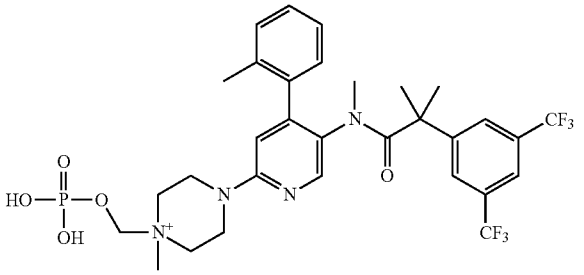
1. A pharmaceutically acceptable salt of a compound of formula GA1:

GA1



2. A method of treating emesis, bladder dysfunction, depression or anxiety in a patient, comprising administering to said patient in need thereof a therapeutically effective amount of a compound of formula GA1:

GA1



or a pharmaceutically acceptable salt thereof.

3. The method of claim **2**, wherein the patient is a human.

4. The method of claim **2**, wherein said compound, or pharmaceutically acceptable salt thereof, is intravenously administered at a dosage of from 10 mg to 200 mg.

5. The method of claim **2**, wherein said emesis comprises chemotherapy induced nausea and vomiting, radiation therapy induced nausea and vomiting, or post-operative nausea and vomiting.

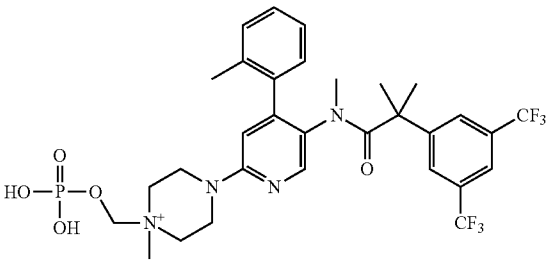
6. The method of claim **2**, wherein said emesis is induced by moderately or highly emetogenic chemotherapy.

7. The method of claim **2**, wherein said emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy.

8. The method of claim **2**, wherein said emesis is acute and delayed emesis induced by moderately or highly emetogenic chemotherapy, further comprising administering ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof and a corticosteroid.

9. A method for making a compound of formula GA1:

GA1



comprising

(a) reacting 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide with chloromethyl di-tert-butyl phosphate in the presence of a polar aprotic solvent; and

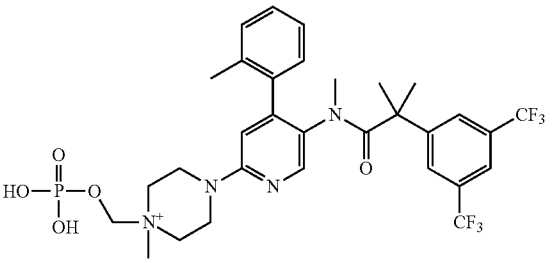
(b) isolating the compound of formula GA1.

10. The method of claim **9**, wherein step (a) is carried out in the presence of an iodide salt and in the absence of a proton scavenger.

11. The method of claim **9**, wherein step (a) is carried out in the absence of air and oxygen.

12. A method for stabilizing a compound of formula GA1:

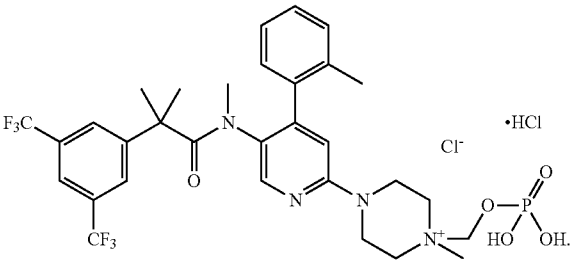
GA1



comprising contacting the compound with two equivalents of hydrochloric acid.

13. The method of claim **12**, wherein the hydrochloric acid is 4M hydrochloric acid.

14. A compound having the following formula:



* * * * *

Exhibit E

US009908907B2

(12) **United States Patent**
Fadini et al.

(10) **Patent No.: US 9,908,907 B2**
(45) **Date of Patent: *Mar. 6, 2018**

(54) **SUBSTITUTED PIPERAZINIUMS FOR THE TREATMENT OF EMESIS**

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(72) Inventors: **Luca Fadini**, Giubiasco (CH); **Peter Manini**, Giubiasco (CH); **Claudio Pietra**, Como (IT); **Claudio Giuliano**, Como (IT); **Emanuela Lovati**, Mendrisio (CH); **Roberta Cannella**, Varese (IT); **Alessio Venturini**, Varese (IT); **Valentino J Stella**, Lawrence, KS (US)

(73) Assignee: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/194,984**

(22) Filed: **Jun. 28, 2016**

(65) **Prior Publication Data**

US 2017/0050993 A1 Feb. 23, 2017

Related U.S. Application Data

(63) Continuation of application No. 14/360,991, filed as application No. PCT/US2012/066778 on Nov. 28, 2012, now Pat. No. 9,403,772, which is a continuation-in-part of application No. 13/478,361, filed on May 23, 2012, now Pat. No. 8,426,450.

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**

A61K 31/496	(2006.01)
A61K 31/4427	(2006.01)
C07D 213/74	(2006.01)
C07D 401/04	(2006.01)
C07F 9/6509	(2006.01)
A61K 31/56	(2006.01)
A61K 45/06	(2006.01)
C07D 213/89	(2006.01)
A61K 31/44	(2006.01)
A61K 31/473	(2006.01)
A61K 31/675	(2006.01)

(52) **U.S. Cl.**

CPC ***C07F 9/650952*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 45/06*** (2013.01); ***C07D 213/74*** (2013.01); ***C07D 213/89*** (2013.01); ***C07D 401/04*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/4427; A61K 31/496; C07D 213/74; C07D 401/04

USPC 514/253.01, 352; 544/360; 546/304

See application file for complete search history.

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Kramer et al., "Distinct Mechanism for Antidepressant Activity by Blockade of Central Substance P Receptors." Science 281(5383),1640-1645 (1998).

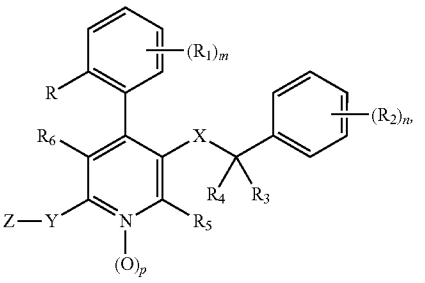
(Continued)

Primary Examiner — Douglas M Willis
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan

(57) **ABSTRACT**

Disclosed are compounds, compositions and methods for the prevention and/or treatment of diseases which are pathophysiologically mediated by the neurokinin (NK_1) receptor. The compounds have the general formula (I):

Fromula (I)



6 Claims, 1 Drawing Sheet

(56) **References Cited**

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Gesztesi et al., "Substance P (Neurokinin-1) Antagonist Prevents Postoperative Vomiting after Abdominal Hysterectomy Procedures." Anesthesiology 93 (4), 931-937 (2000).

Japanese Office Action dated Aug. 25, 2015, which issued during prosecution Japanese Application No. 2014-210716, which corresponds to the present application.

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Hoffmann T et al: "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists", Bioorganic & Medicinal Chemistry Letters, Pergamon, Elsevier Science, GB, vol. 16, No. 5, Mar. 1, 2006; pp. 1362-1365.

Maria Pia Catalani et al: "Identification of novel NK/NKdual antagonists for the potential treatment of schizophrenia", Bioorganic & Medicinal Chemistry Letters, Pergamon, Elsevier Science, GB, vol. 21, No. 22, Jul. 29, 2011, pp. 6899-6904.

Germano Giuliani et al: "Non-peptide NKreceptor ligands based on the 4-phenylpyridine moiety", Bioorganic & Medicinal Chemistry, Pergamon, GB, Pergamon, GB, Feb. 18, 2011, pp. 2242-2251.

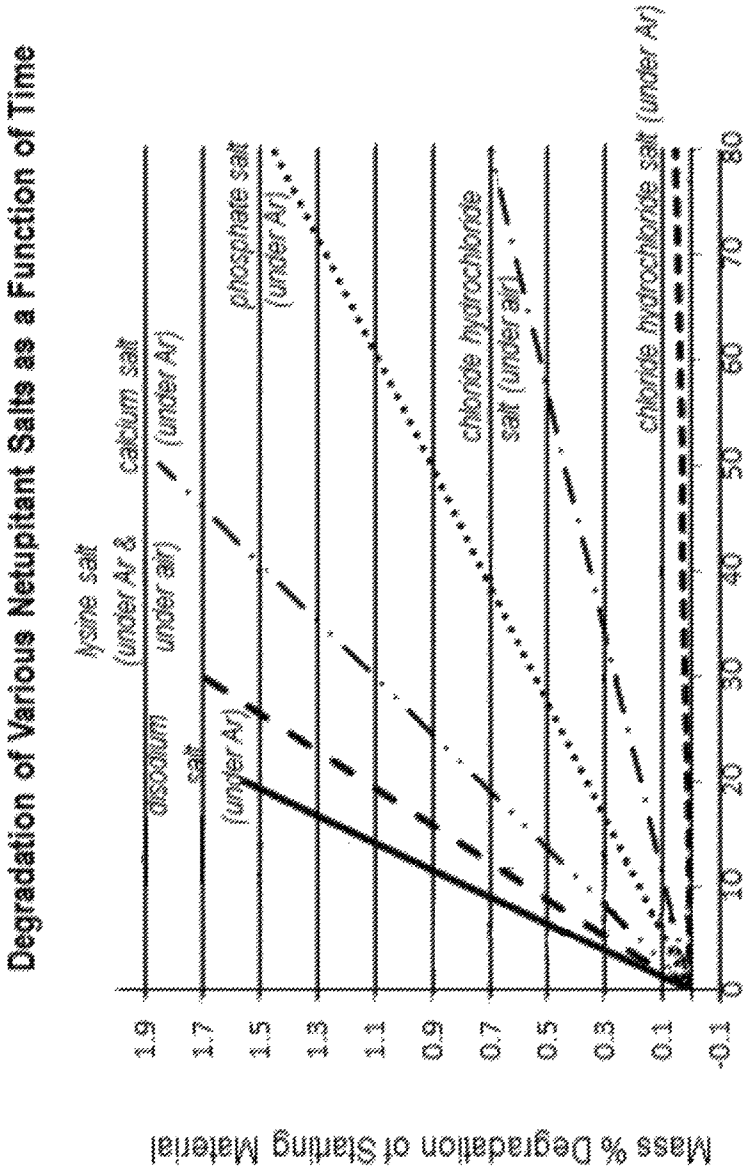


FIGURE 1: Degradation Behavior Over Time for Vaious Salts of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phos-phonooxy)methyl)piperazin-1-ium.

SUBSTITUTED PIPERAZINIUMS FOR THE TREATMENT OF EMESIS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

Description of Related Art

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et al. (*Science* 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis. Gesztesi et al. (*Anesthesiology* 93(4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis.

U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron (a $5\text{-}HT_3$ receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-oxide derivatives are reported in the '026 patent.

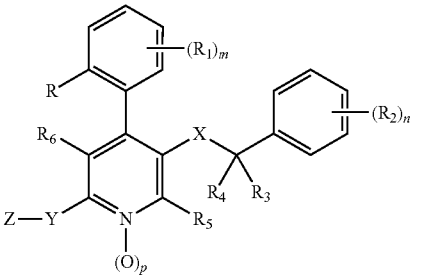
U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclose how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as prodrug structure(s), prodrug stability, synthetic cost, and selectivity of the phosphoryloxymethylation protocol.

In view of the above, there is a need to find new derivatives of and methods for making 4-phenyl-pyridine compounds that are effective NK_1 receptor antagonists, and that have enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives that are particularly well-suited for antagonizing the NK_1 receptor and that have the following general formula (I):

Formula (I)



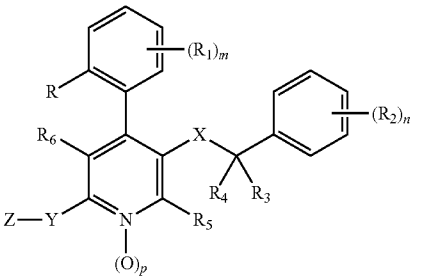
and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK_1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK_1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically-acceptable excipients.

In one embodiment the invention is a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof,

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$,

—SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

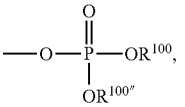
Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:

(Ia) —O^-,

(Ib) —OR^{100},

(Ic)



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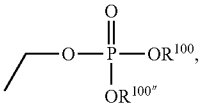
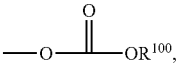
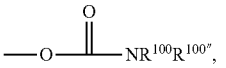


(Ie)



-continued

(If)

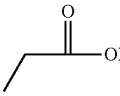


(Ig)

(Ih)

and

(Ii)



where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{103}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

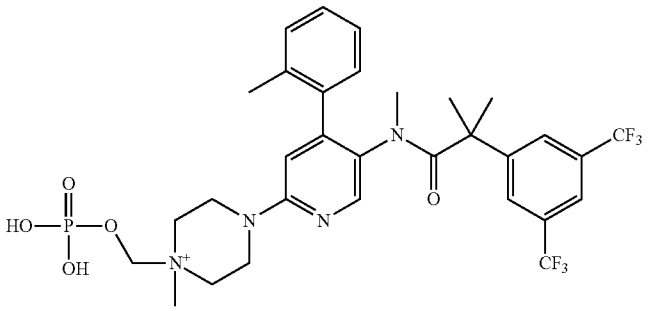
with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one.

In another embodiment the invention is the use of a therapeutically effective amount of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or adduct thereof, in the manufacture of a medicament which is able to treat emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof.

In an alternative embodiment the invention is a method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) as defined above.

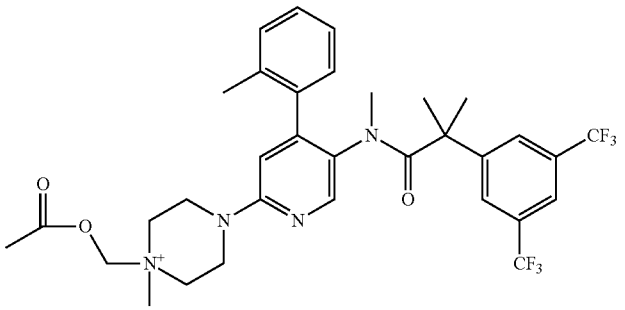
In still another embodiment the invention is a compound selected from the group consisting of:

GA1



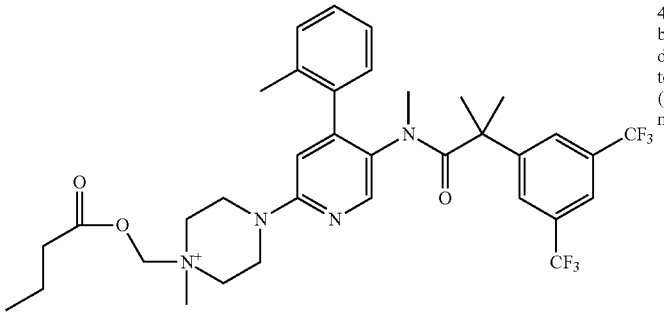
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,

GA2



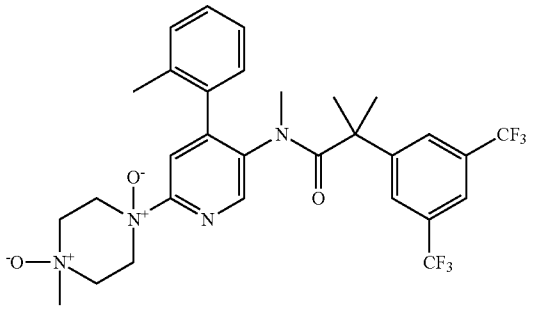
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,

GA3



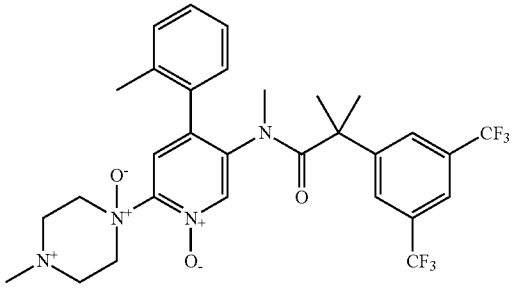
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperaizn-1-ium,

GA4



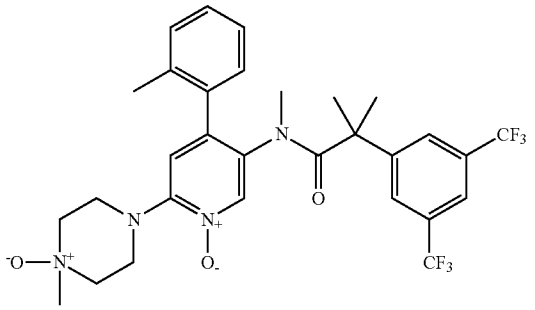
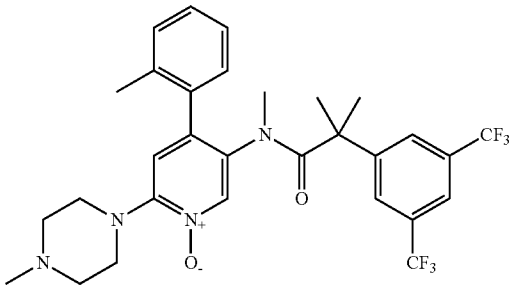
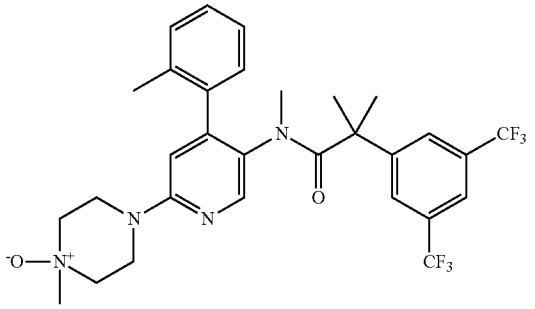
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

GA5



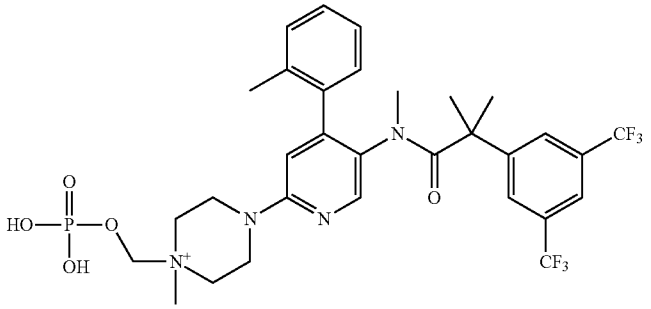
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

-continued

GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

or a pharmaceutically acceptable salt or adduct thereof.

In a further embodiment the invention is a compound of formula GA1.

formula GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanmido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium

or a pharmaceutically acceptable salt or adduct thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** reproduces stability data for various salts of 4-(5-(2-(3,5-bis(trifluoro-methyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphornooxy)methyl)piperazin-1-ium.

DETAILED DESCRIPTION

Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood

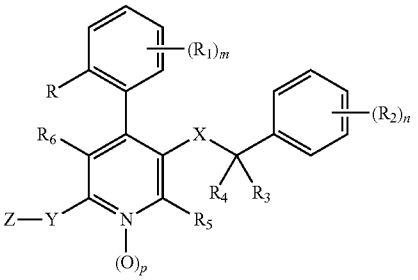
that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —S(O)2R^{102}, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents:

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroaryl alkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituents) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

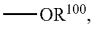
R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —C(O)$NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

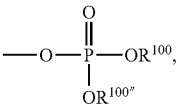
X is selected from the group consisting of —C(O)$NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101} alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

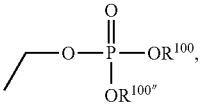
Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

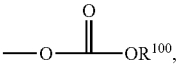
Z is a structural formula selected from the group consisting of:

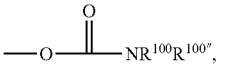
(Ia)

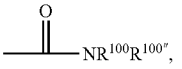

(Ib)


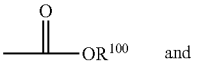
(Ic)


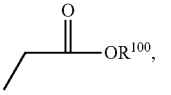
(Id)


(Ie)


(If)


(Ig)


(Ih)

and

(Ii)


where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —C(O)$NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R_{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or

more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

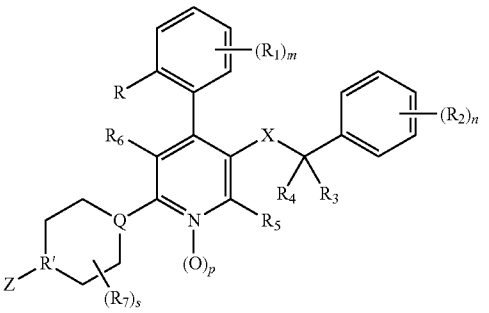
R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is from 0 to 4; n is from 0 to 5; p is from 0 to 1; and with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein X is —$NR^{101}C(O)$. In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

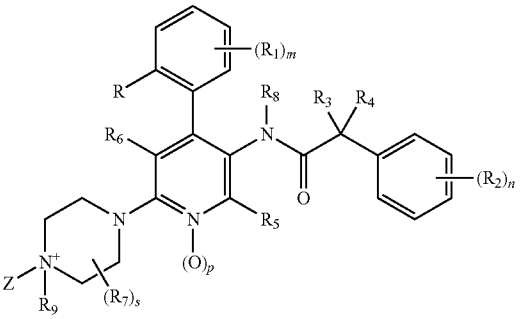
Formula (II)



where Q and R' are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

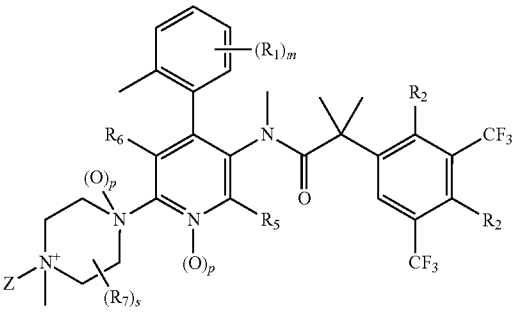
Formula (III)



where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

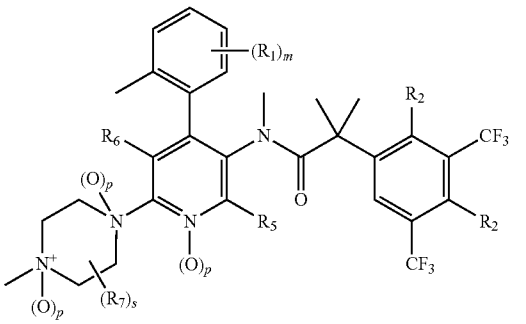
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

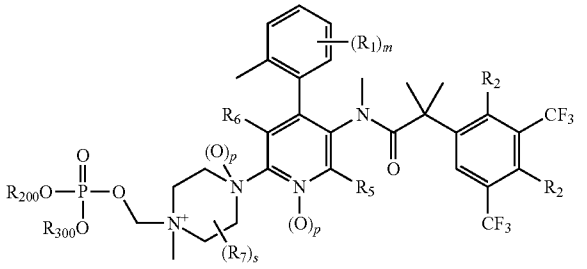
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (VI):

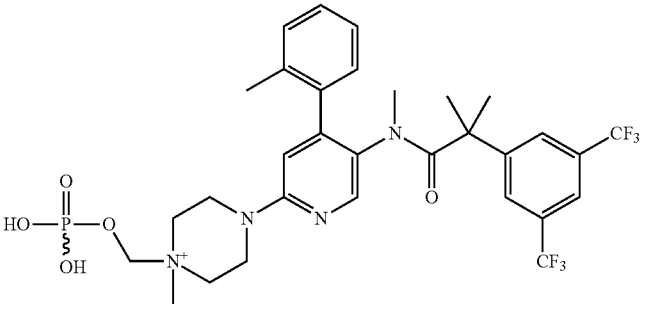
Formula (VI)



where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

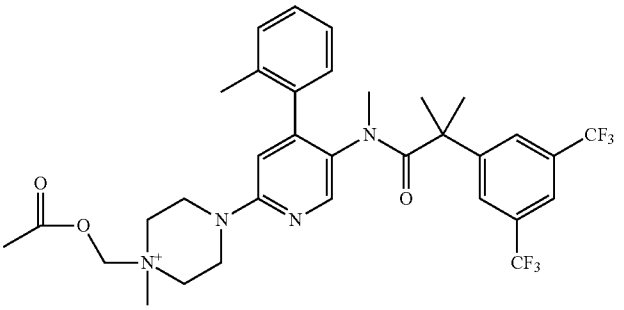
In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of:

GA1



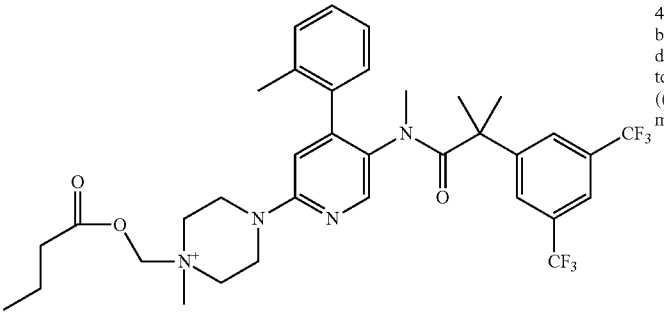
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphoonooxy)methyl)piperazin-1-ium,

GA2



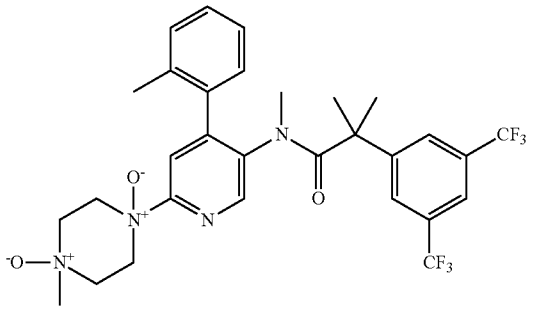
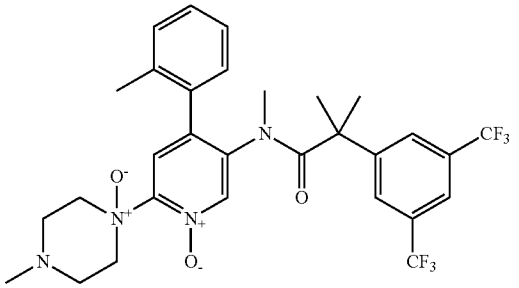
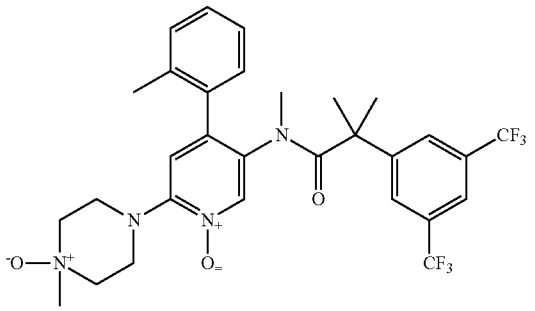
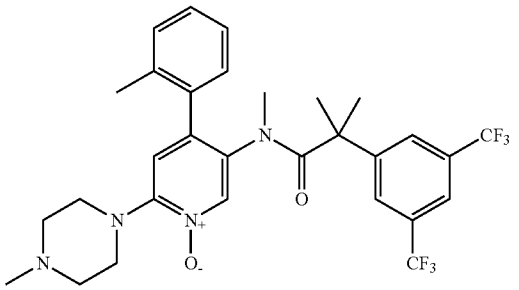
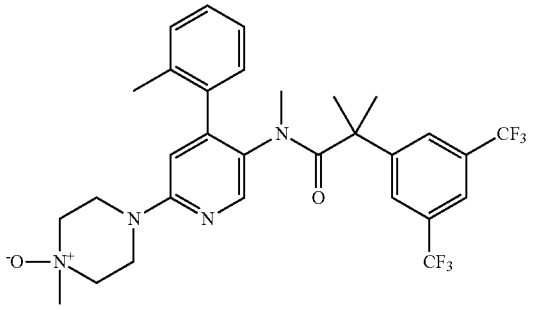
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,

GA3

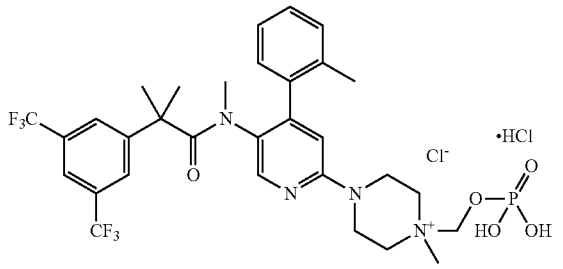


4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,

-continued

GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,
GA5		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,
GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpipearizne 1-oxide.

A particular preferred compound is the chloride hydrochloride HCl salt of GA1having the following chemical structure which, it has been found, is tremendously resistant to decoupling of the oxo-phosphonomethyl, and reversion of the active moiety to its parent state.



Salts and Adducts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced storage stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamide, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamide, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

The disclosed compositions and compounds can be used in the form of adducts derived by formation of Lewis pairs, covalently linked adducts e.g. between N atoms and carbonyl-containing reactants, hydrates and alcoholates, host-guest adducts containing molecular species not bonded or associated with the medicinal compound, and other clathrates.

Depending on the particular compound, an adduct of the compound can be advantageous due to one or more of the adduct's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil, in some instances, an adduct of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where an adduct is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the adduct preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable adduct" refers to an adduct prepared by combining a compound, such as the disclosed compounds, with a gas, water, solvent, Lewis base, carbonyl-containing molecule, or guest molecule that is generally considered suitable for human consumption. Pharmaceutically acceptable addition species are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the adducts of the disclosed compounds are non-toxic "pharmaceutically acceptable adducts." Adducts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic adducts of the disclosed compounds which are generally prepared by reacting a compound of the invention with a suitable organic or inorganic addition species.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, include those derived from Lewis bases such as boric acid, aluminum hydroxide, organic sulfoxides, organic sulfones, organic sulfonium salts, H_3PO_3, siloxanes, and other Lewis bases.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from covalent bonding between an oxygen, nitrogen or sulfur atom of the compound and carbon dioxide, low alkyl aldehyde or ketone, vanillin, amino acid, or a nucleic acid.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from inclusion of an unbonded gas such as dioxygen, dinitrogen, carbon dioxide, nitrous oxide, ethyl ether, or other gas, contained within but not bonded to a crystalline or amorphous phase of the compound.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from association of a molecule of the compound with water, a pharmaceutically acceptable lower alkyl alcohol, or another pharmaceutically acceptable solvent that is associated in a molecular ratio with the compound.

In one embodiment the adduct is optionally a clathrate.

General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

The invention further provides methods for making suitable prodrugs of the 4-phenyl-pyridine derivatives. In one embodiment the invention provides a one-step, acid-free synthesis for functionalizing tertiary amines by reaction with chloromethyl dialkyl phosphate esters to create (phosphooxy)methyl prodrugs that are substrates for phosphatase enzymes. By contrast the prior art had required multiple synthetic steps for comparable reactions, including requiring the use of proton scavengers during initial reaction and requiring strong acid to deprotect the phosphate group in another step. In another embodiment the invention provides methods for making chloromethyl dialkyl phosphate esters having suitable purity and economy, because the quality of phosphate ester compositions from commercial sources is too low to provide acceptable yields for reactions according to the invention. In an additional embodiment the invention provides a method to stabilize the (phosphooxy)methyl prodrugs according to the invention by combination with two equivalents of hydrochloric acid, because whereas the prior art preferred the use of dibasic salts of (phosphooxy) methyl substituents for quaternary ammonium salts in prodrugs, the present invention had found that such salts are unstable and reform the underlying drug during storage.

Definition of Terms

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms, in one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a

carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y—," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X-Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxy-propyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile") —CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The term "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula —$NH(CH_3)$), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to =O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to =S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxide" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroa-

tom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane, thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2—. The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2—. The term "methylenoxy" refers to the group —CH—O—. The term "methylenethioxy" refers to the group —CH_2—S—. The term "methylenamino" refers to the group —CH_2—N(H)—. The term "ethylenoxy" refers to the group —CH_2—CH_2—O—. The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus,

for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule. If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically-acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active compounds and compositions, for example, can be administered orally, rectally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington; The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E. Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

In some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide$\geq$1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg. orally on day 1, followed by 8 mg. orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously adminis-

tered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-clay course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said 5-HT_3 antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg, or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 ml.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodiment, the netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease. In some other forms, disclosed are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

More Definitions of Terms

1. A, an, the

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes not only single carriers but also mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "ml," for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. In order to more fully document the state of the art to which this invention pertains, the disclosures of these publications are to be considered as being referenced individually, specifically and in their entireties for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

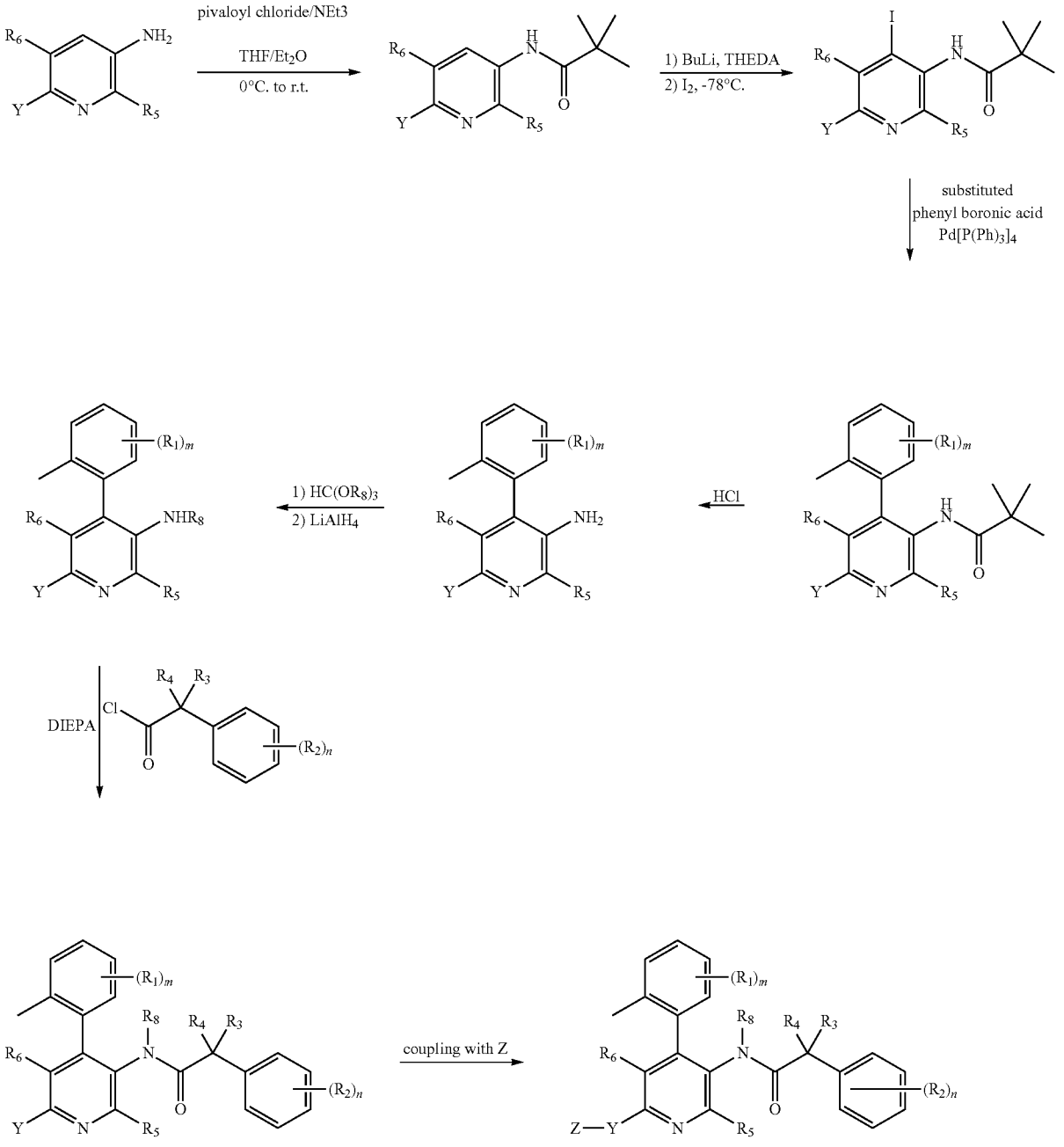
Example 1

Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

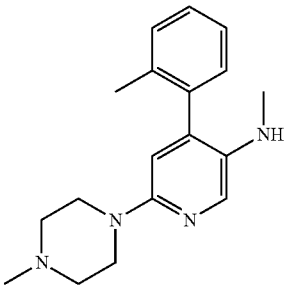
General Scheme of Preparing Compounds of Formula (I)

Scheme 1



Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, which are referenced individually, specifically and in their entireties for the material contained in them that is relevant to the preparation of intermediate I.

Synthesis of Methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THF were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolyl-magnesium chloride solution (1 M in THF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THF removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent:ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution. The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THF were added 3.1 ml (42.0 mMol) thionylchloride and 143 .mu.l (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0° C. After 30 minutes at 0° C., THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as & beige crystalline foam. MS (ISP): 247 (M+H$^+$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamide in 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam, MS (ISP): 311 (M+H$^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol 4:1) to yield 100 mg (70%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 (M+H$^+$, 100), 226 (42).

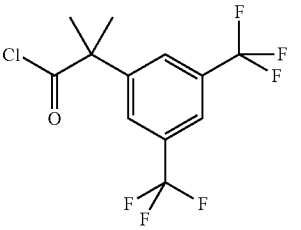
Step 5:

2.15 ml (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH-8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam. MS (ISP): 341 (M+H$^+$, 100), 284 (35).

Step 6:

A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-A1.® (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 (M+H$^+$, 100).

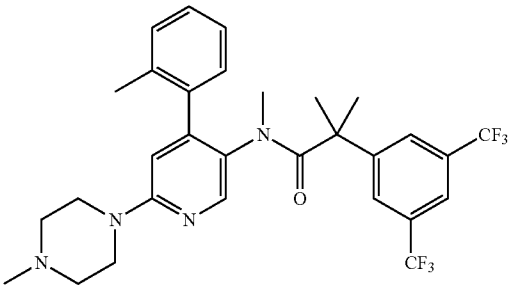
Synthesis of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution

was rotary evaporated to dryness. 9 ml Toluene were added and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, $3H_{arom}$); 1.77 (s, 6H, 2 CH_3).

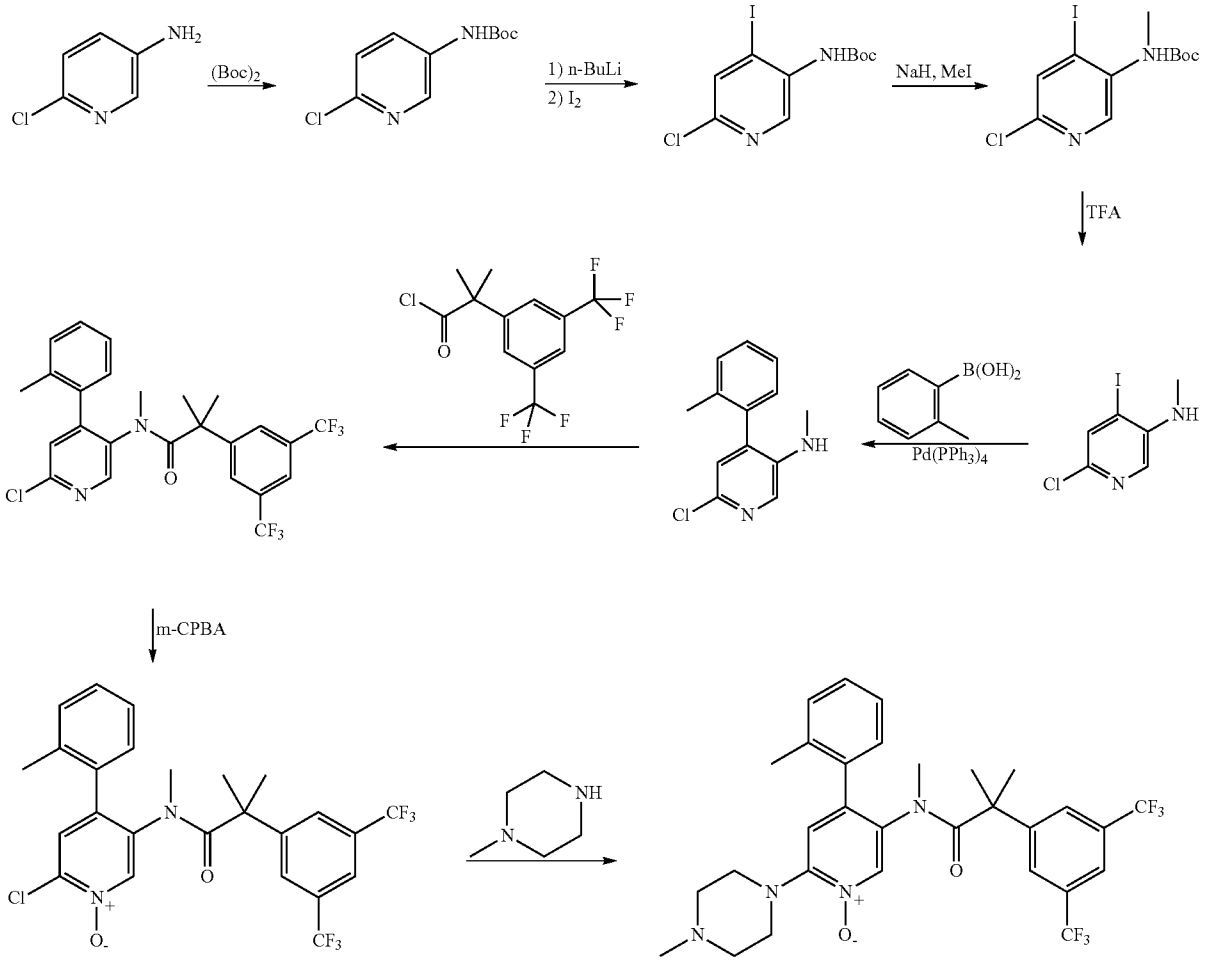
Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)



A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide as white crystals. M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2



Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl (6-chloropyridin-3-yl) carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl (6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THF was added n-BuLi (600 mL, 1.5 mol) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THF was added. Then the solution was stirred at −78° C. for 4 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl (6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 mL of anhydrous THF was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THF was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl (6-chloro-4-iodopyridin-3-yl)(methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 ml of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol). The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)-pyridin-3-yl)-N,2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

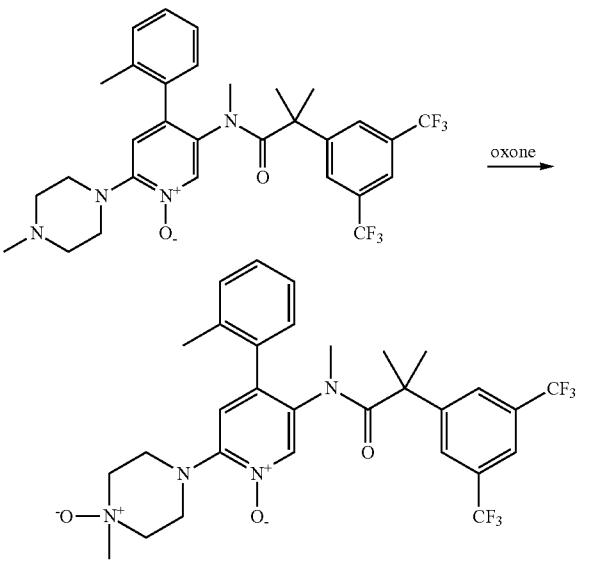
To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature. 1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl) pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45~1.20 (m, 6H).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl) pyridin-2-yl)-1-methylpiperazine 1-oxide

Scheme 3

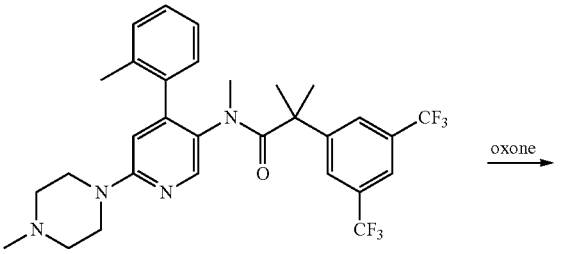


To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 ml of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for

4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). ^{1}HNMR (CDCl3, 400 MHz) S 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37-7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 2H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

Scheme 4



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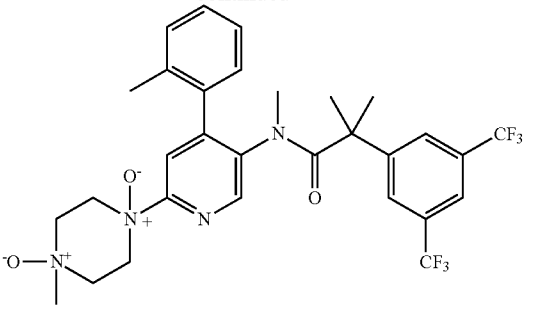
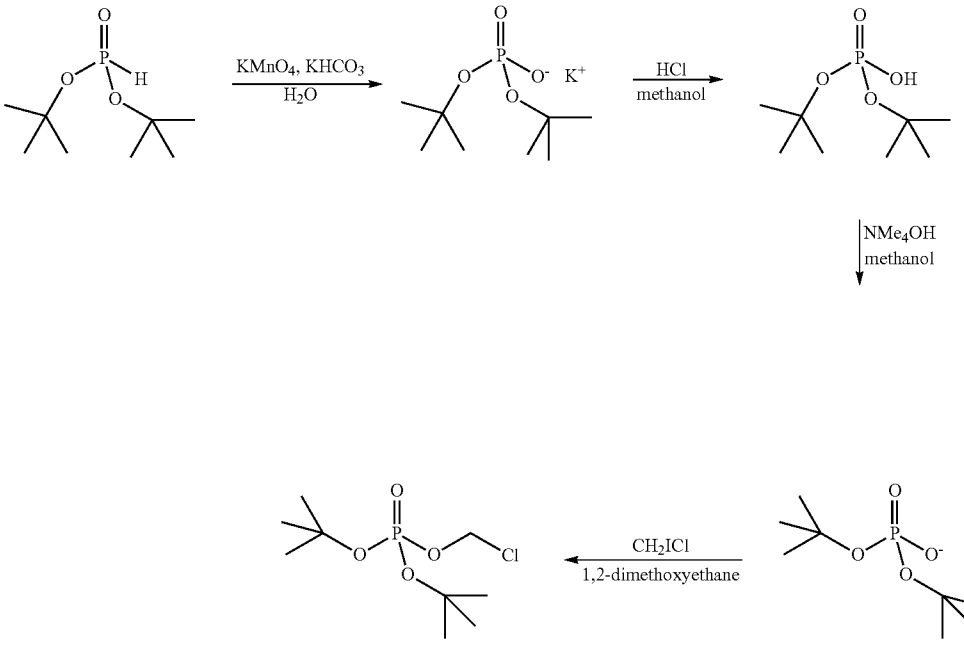


To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (3.38 g, 40.3 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR (CDCl3, 400 MHz, at 333 K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26~7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

Synthesis (A) of Di-tert-butyl (Chloromethyl) Phosphate

Scheme 5



Di-tert-butyl phospohite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time. The reaction as then allowed to continue at room temperature for an additional half hour. Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the crude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloroiodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium without further purifications (60% yield): ^{1H}HNMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

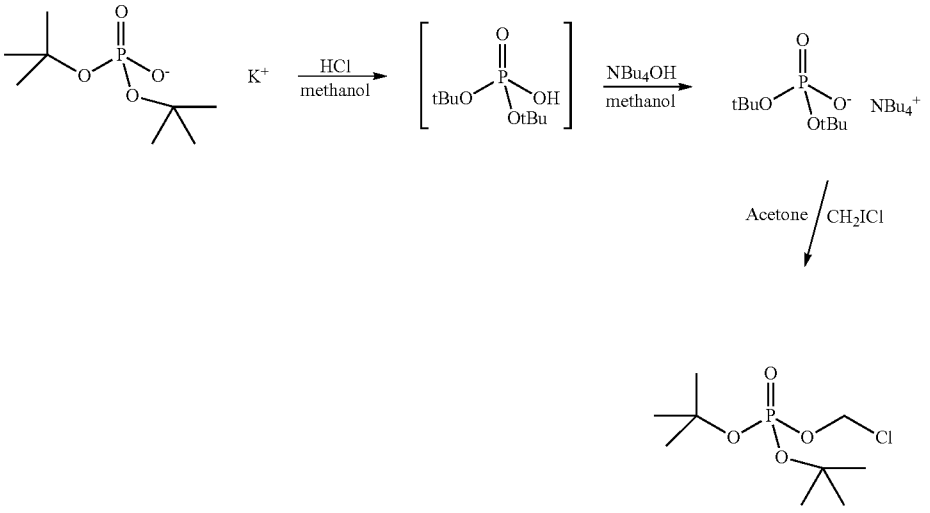
Synthesis (B) of Di-tert-butyl (Chloromethyl) Phosphate

Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) is dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetrabuthylammonium hydroxide 1 M in methanol (20.14 mmole) while keeping the reaction cooled at 0° C. with efficient stirring. The resulting clear solution is placed under reduced pressure to give the intermediate product. The tetrabuthylammonium di-tert-butyl-phosphate dissolved in acetone is then added dropwise to 53.3 grams of chloroiodomethane (302.1 mmole) and stirred at 40° C. for 1-2 hours. The solvent and excess of chloroiodomethane are distilled off, the reaction mass suspended in TBME and then filtered. The filtrate is washed by a saturated solution of sodium bicarbonate and water and then placed under reduced pressure to substitute the solvent by acetone, i.e., to remove the solvent after which it is replaced with acetone. The chloromethyl di-tert-butyl phosphate 7-20% in acetone is used in the next step without further purifications (70-80% yield): 1H-NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

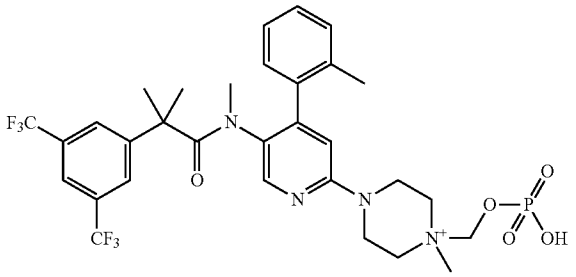
Stability Studies of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)(pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium Salts

In order to further improve the stability and solubility of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium, a variety of its derivative salts were synthesized and tested. Their synthesis employed either a) neutralization of the dried diacid phosphate species and its corresponding base salts or b) a direct acid deprotection starting from the dried di(tert-butyl)-protected phosphate species. Neutralization was performed with L-histidine, magnesium salt, N-methyl-D-glucamine (dimeglumine), and L-lysine. Both procedures were tried in

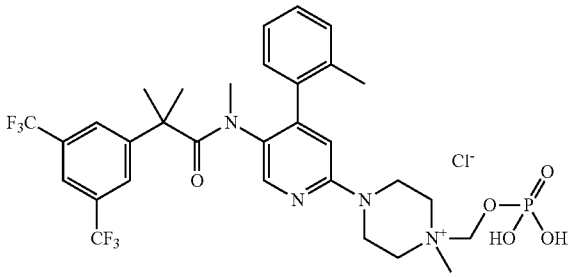
Scheme 5A



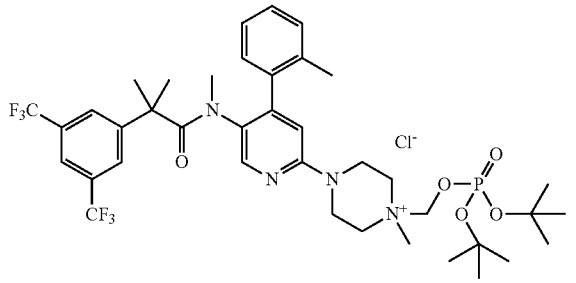
the synthesis of citric derivatives whereas with other acids the direct deprotection reaction was used. The figures below show the most relevant structures.



Parent acid species



Diacid phosphate species



Protected phosphate species

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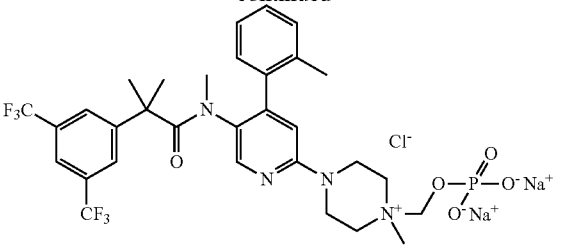
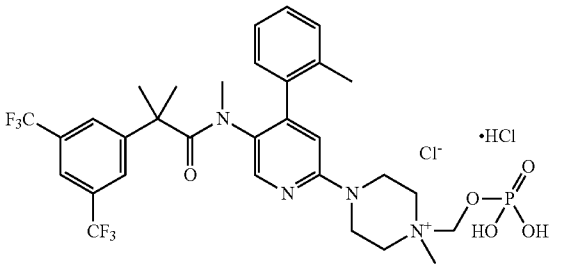


Dibasic phosphate species



Chloride hydrochloride species

When the parent acid species was not stored in dry condition it was found to undergo over 8% degradation in the first week and over 65% degradation in the first six months. When the dried parent acid species was held at 30° C. in air it underwent 0.05% degradation in the first 7 days and at total of 7.03% degradation in six months. When the dried parent acid species was held under argon at room temperature it underwent up to 0.13% degradation in the first 7 days but then was essentially stable for six months. Results for various derivative salts are shown in Table 1 below.

TABLE 1

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	L-Histidine, 2 eq.	26.6%	95.94%	Degradation: +0.70% in 6 days (in air) +0.46% in 6 days (in argon)
MeOH	$Mg(OH)_2$, 2 eq.	48.6%	94.11%	Degradation: +0.81% in 6 days (in air) +0.29% in 6 days (in argon)
MeOH + DCM, 1:1	Citric acid, 2 eq.	N.A.	94.40%	From protected species.
MeOH	1. HCl dioxane, 4 eq. 2. $Ca(OH)_2$	>90%	94.50%	From protected species.
MeOH	H_3PO_4, 85%, 2 eq.	>90%	98.81%	From protected species and retains 0.39% of that species.
MeOH	HBr, 48%, 4 eq.	84.6%	96.11%	From protected species. Product degrades rapidly.
MeOH + DCM, 1:4	CH_3SO_3H	N.A.	61.54%	From protected species. Product NOT stable: contains 32.45% decomposition species.
MeOH	NaH_2PO_4, 4 eq.	N.A.	n.d.	Only 1.27 of parent species formed. Poor reaction.

TABLE 1-continued

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	N-methyl-D-glucamine (Meglumine), 2 eq.	N.A.	96.88%	Degradation: +0.87% in 6 days (in air) +1.52% in 11 days (in argon)
MeOH	N-methyl-D-glucamine (Meglumine), 1 eq.	>99%	97.42%	Degradation: +0.77% in 6 days (in air) +0.83% in 7 days (in argon)
MeOH + DCM, 5:2	1. NaOH, 3 eq 2. Citric acid, 1 eq.	96.5%	97.49%	Degradation: +0.09% in 2 days (in argon) +0.59% in 89 days (in argon)
MeOH + DCM, 5:2	1. NaOH, 3 eq, 2. Fumaric acid, 1 eq.	93.8%	97.46%	Degradation: +1.95% in 14 days (in air) +1.80% in 12 days (in argon)
MeOH	L-lysine, 1 eq.	>99%	97.62%	Degradation: +0.69% in 14 days (in air) +0.48% in 12 days (in argon)

A more comprehensive showing of stability results is given in FIG. **1**, where the horizontal axis represents number of days of testing and the vertical axis represents the mass percent of degradation. Alphabetical letters are used to denote data points on the graph that correspond to degradation percentage values over time for respective salts of the same parent compound as just described above and in Table 2 below. The drawn lines correspond to general trends over periods of days for the benchmark salt (the disodium salt) and for the few salts that manifested more desirable results than the disodium salt.

TABLE 2

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
a	2 Dimeglumine	Air
b	2 Dimeglumine	Argon
c	Dimeglumine	Air
d	Dimeglumine	Argon
e	Lysine	Air
f	Lysine	Argon
g	Fumarate	Air
h	Fumarate	Argon
i	Citrate	Air

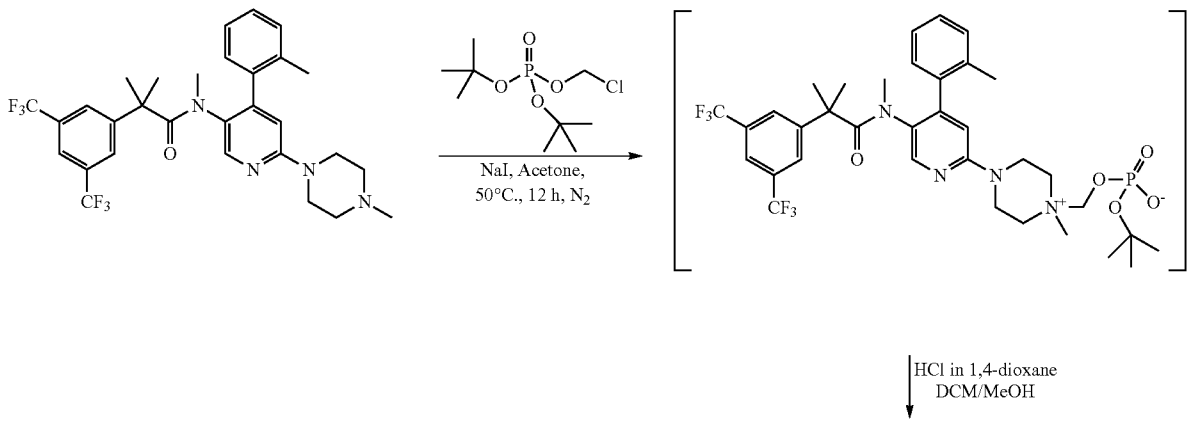
TABLE 2-continued

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
j	Citrate	Argon
k	Bromide	Air
l	Bromide	Argon
m	Mesylate	Nitrogen
n	Phosphate	Air
o	Phosphate	Argon
p	Citrate	Nitrogen
q	Calcium	Air
r	Calcium	Argon
s	Chloride hydrochloride, anhydrous	Air
t	Chloride hydrochloride, anhydrous	Argon
u	Disodium salt	Air
v	Histidine	Air
w	Histidine	Argon
x	Magnesium	Air
y	Magnesium	Argon

Synthesis (A) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium Chloride Hydrochloride

Scheme 6



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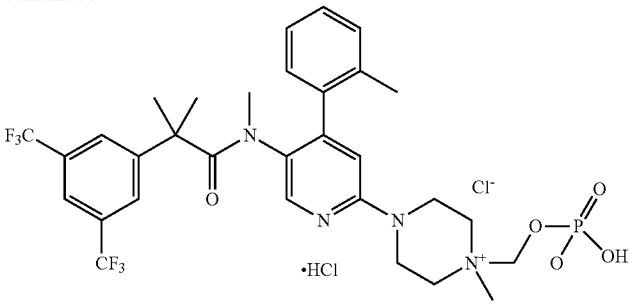
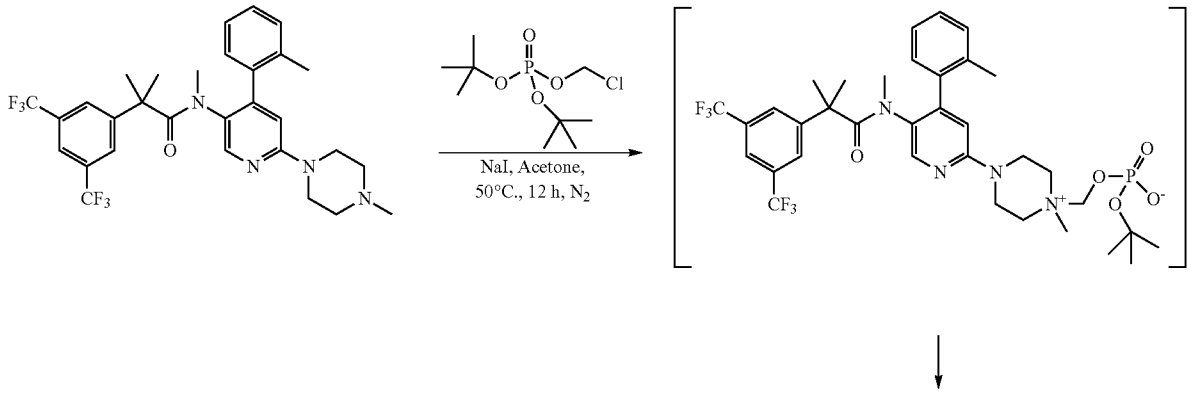


The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile. 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphtalene and 46.6 g (80.54 mmole) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropyl ether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropylether/acetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-7.10 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m, 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4 M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride as white solid (Yield: 88-93%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

Synthesis (B) of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium Chloride Hydrochloride

Scheme 6A



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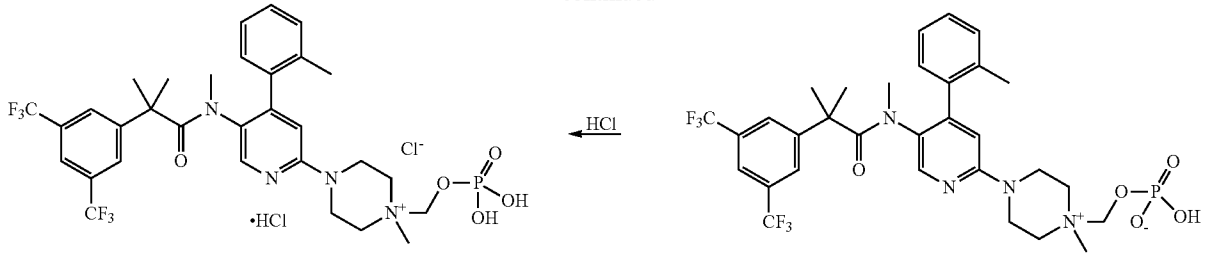


To the solution of chloromethyl di-tert-butyl phosphate in Acetone (22.1 g from a 10% solution, 85.58 mmole), 15.5 g (103.24 mmole) of sodium iodide and 33.0 g (57.00 mmole) of netupitant were added and the solution heated at 50° C. for at 6-16 h. The precipitated salts were filtered off, the acetone distilled under reduced pressure and the crude product dissolved in 43.0 g of methanol and 43.0 g 1,4-dioxane. 12.6 g of HCl 4 M in dioxane (113.85 mmole) were added, and then methanol is distilled off at 40° C. under reduced pressure. The solution is cooled at 5° C. and stirred at 5° C. for at least 2 h at 5° C. The product was isolated by filtration, purified by additional slurry in acetone (238 g), and filtered and washed with acetone (47 g) and pentane (2×72 g).

The product was finally dried under reduced pressure at 60° C. to afford 22-30 g of white-yellowish solid (Yield: 50-70%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

It is to be understood that the product shown in Scheme 6A is illustrative, being just one of several permutations in which the acidic protons bond to various atoms in an equilibrium. For instance depiction of other permutations would show a proton bound to one or more of the N atoms while one or more of the O atoms bound to the P atom would bear an anionic charge. The invention comprises all of the molecular species within that equilibrium and the product shown in the FIGURE is intended to represent all of them in a generic fashion.

7. Evaluation of Representative Compounds of Formula (I)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 3 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE 3

Chemical Stability and Solubility of Representative Compounds

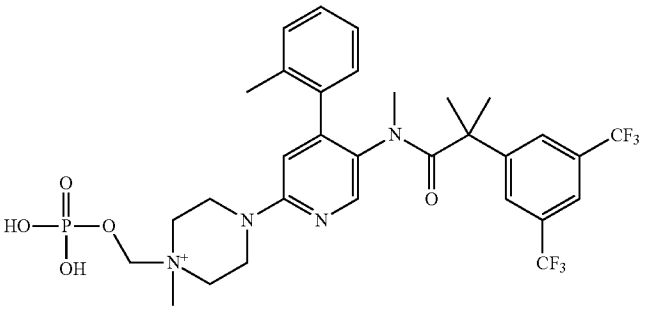
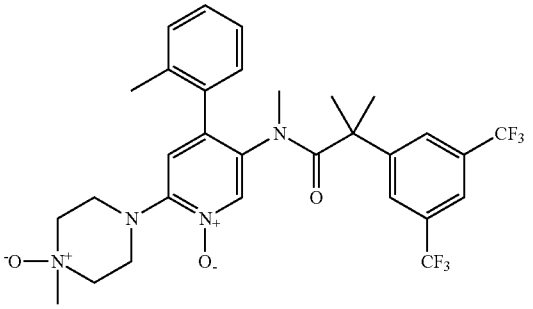
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1		medium	10-15 mg/ml
2		high	>10 mg/ml

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

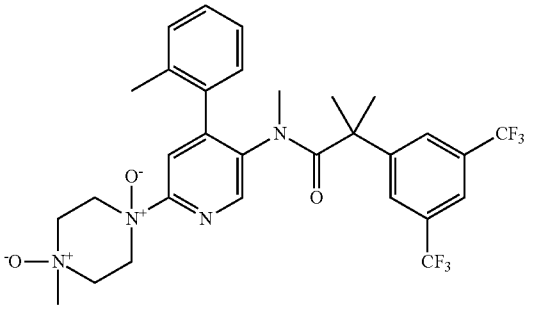
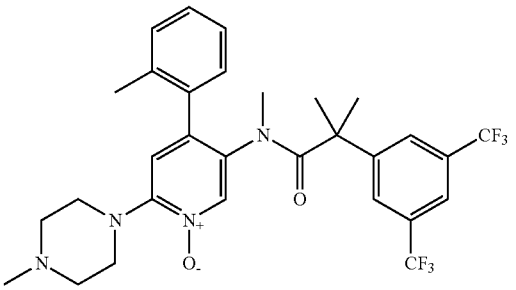
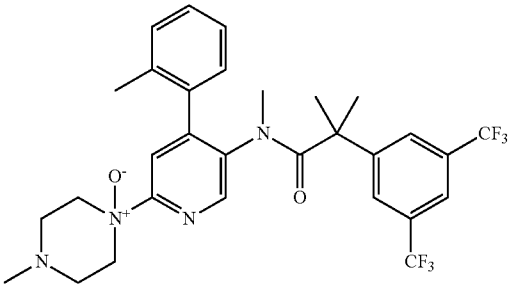
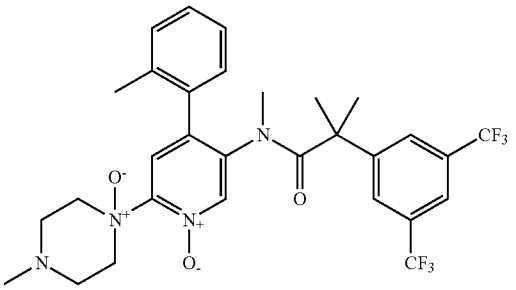
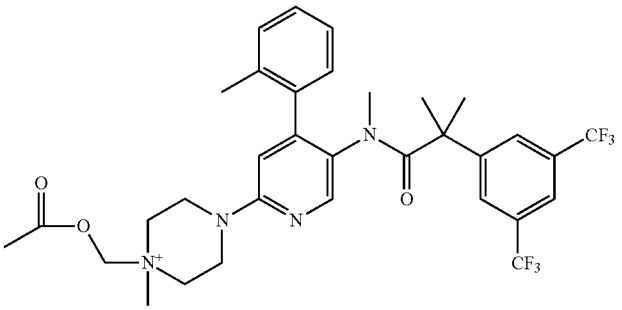
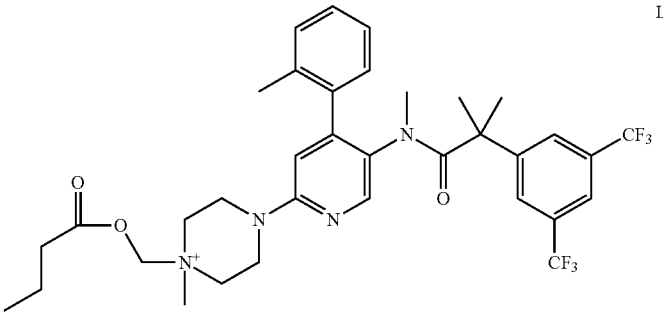
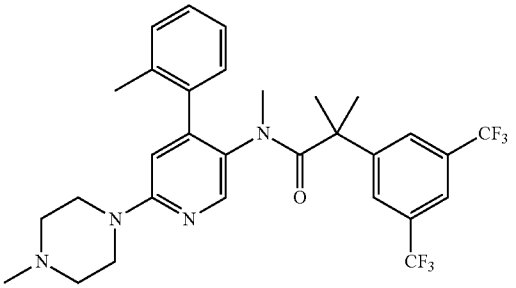
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
3		high	>10 mg/ml
4		medium	~0.6 mg/ml
5*		medium	~1 mg/ml
6		low	N/A
7		low	insoluble

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
8		Low	insoluble
9*			0.25

*Reference Compound

ii. Local Tolerance

In contrast to netupitant (compound no. 9 in the above table), seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

- There were minimal signs of inflammation at injection site and there was little edema;
- No later stage thrombus was found in any animal studied;
- Severity of inflammation was similar in compound and vehicle-treated animals;
- No tissue necrosis was observed in any of the tails; and
- The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 3), as compared to a reference compound—netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a close volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Before administration, rats were fasted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pre-dose and at 0.05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma, samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO:Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solu-

bility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (IV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, 15 and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC. MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 3, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 4:

TABLE 4

Comparative Bioequivalence Studies of Netupitant and Related Compounds

	IV			PO
	Compound 1	Compound 2	Compound 3	Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng · min/ml)	315627	88732	192730	307285
Bioequivalence (%)	103	29	63	

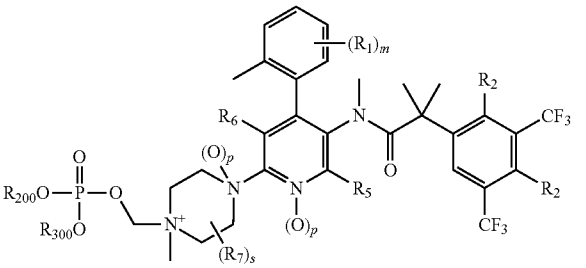
*Reference Compound

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby referenced individually and specifically for the material contained in them that is discussed in the sentence in which the reference is relied upon. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound of formula (VI):

(VI)



or a pharmaceutically acceptable salt thereof, wherein:

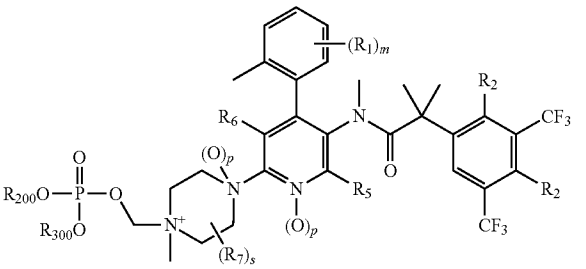
(a) R_2, R_5 and R_6 are each independently hydrogen;

(b) m, p and s are each independently zero; and

(c) R_{200} and R_{300} are each independently selected from the group consisting of hydrogen and methyl.

2. A chloride hydrochloride salt of a compound of formula (VI):

(VI)



wherein:

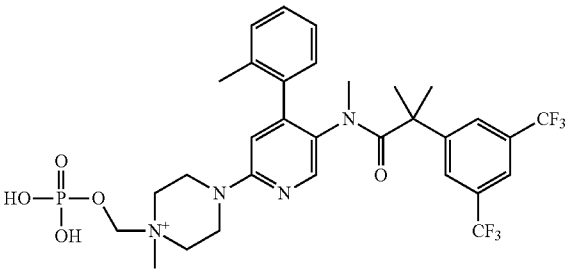
(a) R_2, R_5 and R_6 are each independently hydrogen;

(b) m, p and s are each independently zero; and

(c) R_{200} and R_{300} are each independently selected from the group consisting of hydrogen and methyl.

3. A parenteral pharmaceutical composition comprising a compound of formula (I):

(I)

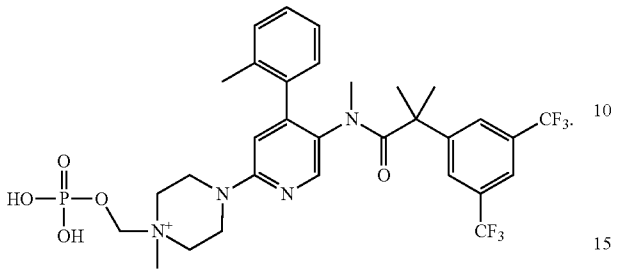


or a pharmaceutically acceptable salt thereof, and one or more liquid pharmaceutical excipients.

4. The parenteral composition of claim **3**, wherein the parenteral composition further comprises palonosetron, or a pharmaceutically acceptable salt thereof.

5. A parenteral pharmaceutical composition comprising a chloride hydrochloride salt of a compound of formula (I):

(I)



and one or more liquid pharmaceutical excipients.

6. The parenteral composition of claim 5, wherein the parenteral composition further comprises palonosetron, or a pharmaceutically acceptable salt thereof.

* * * * *

Exhibit F

US010208073B2

(12) **United States Patent**
Fadini et al.

(10) **Patent No.: US 10,208,073 B2**
(45) **Date of Patent: Feb. 19, 2019**

(54) **SOLUTION COMPRISING THE CHLORIDE HYDROCHLORIDE SALT OF 4-(5-(2-(3,5-BIS (TRIFLUOROMETHYL)PHENYL)-N,2-DIMETHYLPROPANAMIDO)-4-(O-TOLYL) PYRIDIN-2-YL)-1-METHYL-1-((PHOS-PHONOOXY)METHYL)PIPERAZIN-1-IUM-(FOSNETUPITANT) AND PALONOSETRON HYDROCHLORIDE IN COMBINATION WITH DEXAMETHASONE AS A NEUROKININ RECEPTOR MODULATOR**

(71) Applicant: **HELSINN HEALTHCARE SA**, Lugano/Pazzallo (CH)

(72) Inventors: **Luca Fadini**, Giubiasco (CH); **Peter Manini**, Giubiasco (CH); **Claudio Pietra**, Como (IT); **Claudio Giuliano**, Como (IT); **Emanuela Lovati**, Mendrisio (CH); **Roberta Cannella**, Varese (IT); **Alessio Venturini**, Varese (IT); **Valentino J Stella**, Lawrence, KS (US)

(73) Assignee: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/874,325**

(22) Filed: **Jan. 18, 2018**

(65) **Prior Publication Data**

US 2018/0194788 A1 Jul. 12, 2018

Related U.S. Application Data

(63) Continuation of application No. 15/194,984, filed on Jun. 28, 2016, now Pat. No. 9,908,907, which is a continuation of application No. 14/360,991, filed as application No. PCT/US2012/066778 on Nov. 28, 2012, now Pat. No. 9,403,772, which is a continuation-in-part of application No. 13/478,361, filed on May 23, 2012, now Pat. No. 8,426,450.

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**

C07D 213/74	(2006.01)
C07D 453/02	(2006.01)
C07J 9/00	(2006.01)
C07F 9/6509	(2006.01)
C07D 401/04	(2006.01)
A61K 31/496	(2006.01)
A61K 31/56	(2006.01)
A61K 45/06	(2006.01)
C07D 213/89	(2006.01)
A61K 31/44	(2006.01)
A61K 31/473	(2006.01)
A61K 31/675	(2006.01)

(52) **U.S. Cl.**

CPC ***C07F 9/650952*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 45/06*** (2013.01); ***C07D 213/74*** (2013.01); ***C07D 213/89*** (2013.01); ***C07D 401/04*** (2013.01)

(58) **Field of Classification Search**

CPC C07D 213/74; C07D 453/02; C07J 9/00
USPC 544/360; 546/133; 552/553
See application file for complete search history.

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Krise, Jeffrey P. et al., Novel Prodrug Approach for Tertiary Amines. 2. Physicochemichal and In Vitro Enzymatic Evaluation of Selected N-Phosphonooxymethyl Prodrugs; Journal of Pharmaceutical Sciences, vol. 88, No. 9, Sep. 1999, 922-927.

Krise, Jeffrey P. et al., Novel Prodrug Approach for Tertiary Amines. 3. In Vivo Evaluation of Two N-Phosphonooxymethyl Prodrugs in Rats and Dogs; Joumal of Pharmaceutical Sciences, vol. 38, No. 9, Sep. 1999, 928-932.

Kramer et al., "Distinct Mechanism for Antidepressant Activity by Blockade of Central Substance P Receptors." Science 281(5383),1640-1645 (1998).

(Continued)

Primary Examiner — Douglas M Willis
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan

(57) **ABSTRACT**

Disclosed is a solution comprising the chloride hydrochloride salt of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium (fosnetupitant) and palonosetron hydrochloride in combination with dexamethasone and its application in methods for preventing acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy.

13 Claims, 1 Drawing Sheet

(56) **References Cited**

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Gesztesi et al., "Substance P (Neurokinin-1) Antagonist Prevents Postoperative Vomiting after Abdominal Hysterectomy Procedures." Anesthesiology 93 (4), 931-937 (2000).

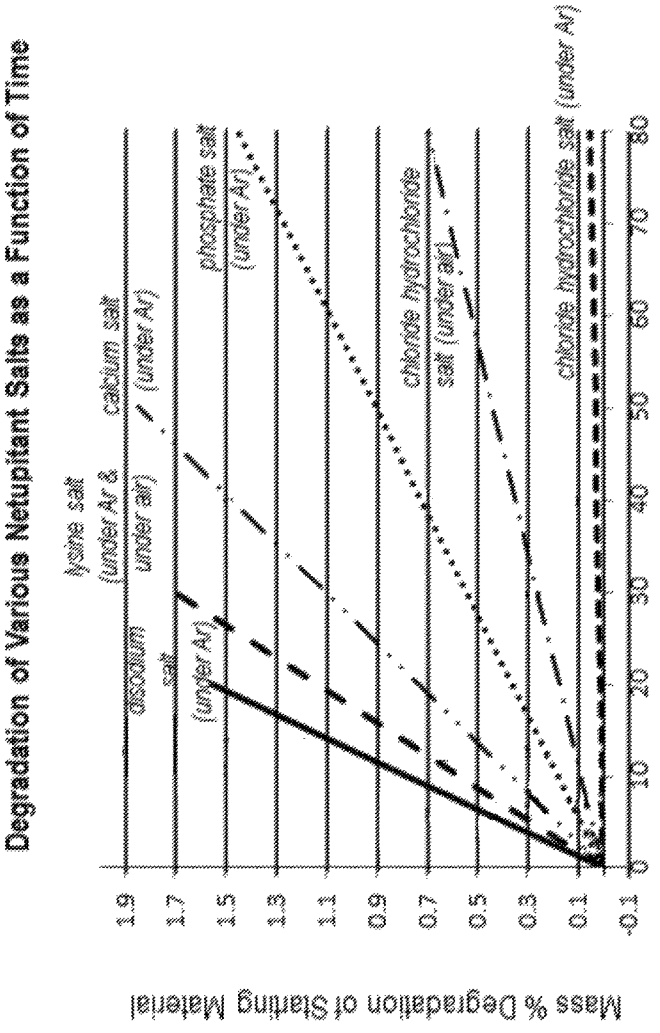
Japanese Office Action dated Aug. 25, 2015, which issued during prosecution Japanese Application No. 2014-210716, which corresponds to the present application.

International Search Report issued in corresponding International Application No. PCT/US2012/066778 dated Jan. 3, 2013.

Hoffmann T et al: "Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists", Bioorganic & Medicinal Chemistry Letters, Pergamon, Elsevier Science, GB, vol. 16, No. 5, Mar. 1, 2006; pp. 1362-1365.

Maria Pia Catalani et al: "Identification of novel NK/NKdual antagonists for the potential treatment of schizophrenia", Bioorganic & Medicinal Chemistry Letters, Pergamon, Elsevier Science, GB, vol. 21, No. 22, Jul. 29, 2011, pp. 6899-6904.

Germano Giuliani et al: "Non-peptide NKreceptor ligands based on the 4-phenylpyridine moiety", Bioorganic & Medicinal Chemistry, Pergamon, GB, Pergamon, GB, Feb. 18, 2011, pp. 2242-2251.



Degradation Behavior Over Time for Vaious Salts of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phos-phonooxy)methyl)piperazin-1-ium.

SOLUTION COMPRISING THE CHLORIDE HYDROCHLORIDE SALT OF 4-(5-(2-(3,5-BIS (TRIFLUOROMETHYL)PHENYL)-N,2-DIMETHYLPROPANAMIDO)-4-(O-TOLYL) PYRIDIN-2-YL)-1-METHYL-1-((PHOSPHONOOXY)METHYL)PIPERAZIN-1-IUM-(FOSNETUPITANT) AND PALONOSETRON HYDROCHLORIDE IN COMBINATION WITH DEXAMETHASONE AS A NEUROKININ RECEPTOR MODULATOR

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

Description of Related Art

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et al. (*Science* 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis. Gesztesi et al. (*Anesthesiology* 93(4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron (a $5\text{-}HT_3$ receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-oxide derivatives are reported in the '026 patent.

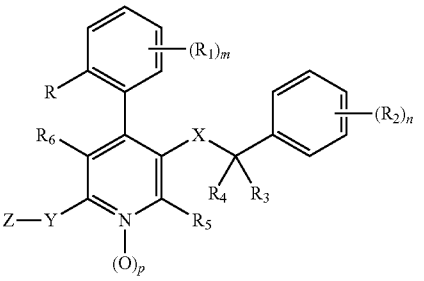
U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclose how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as prodrug structure(s), prodrug stability, synthetic cost, and selectivity of the phosphoryloxymethylation protocol.

In view of the above, there is a need to find new derivatives of and methods for making 4-phenyl-pyridine compounds that are effective NK_1 receptor antagonists, and that have enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives that are particularly well-suited for antagonizing the NK_1 receptor and that have the following general formula (I):

Formula (I)



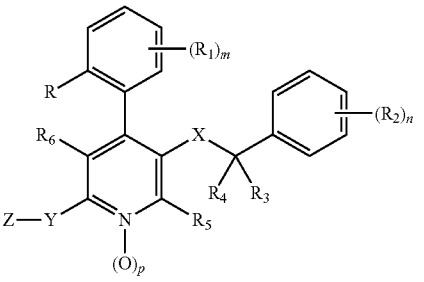
and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK_1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK_1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

In one embodiment the invention is a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof,

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, $C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, $S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, het-

eroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, $NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

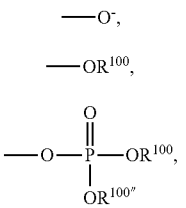
R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, $NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, $NR^{101}C(O)R^{102}$, —$C(O)R^{01}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, $NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:

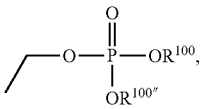


(Ia)

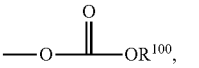
(Ib)

(Ic)

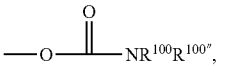
-continued



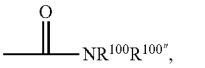
(Id)



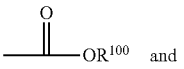
(Ie)



(If)

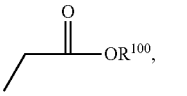


(Ig)



(Ih)

and



(Ii)

where formula (Ia) refers to an oxide;

R^{100}, $R^{100"}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, $NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100"}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

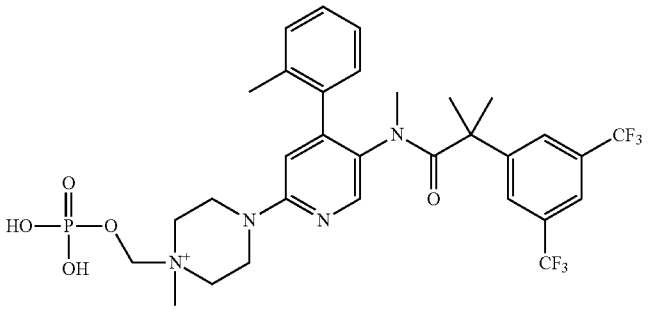
with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one.

In another embodiment the invention is the use of a therapeutically effective amount of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or adduct thereof, in the manufacture of a medicament which is able to treat emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof.

In an alternative embodiment the invention is a method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) as defined above.

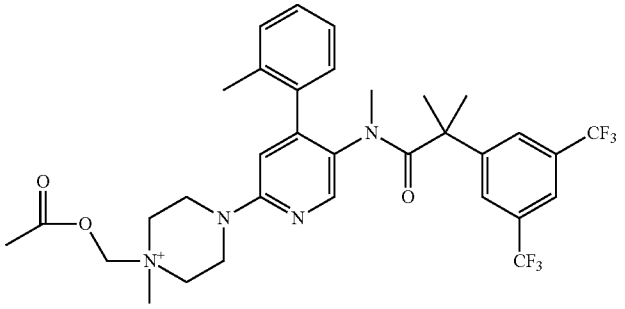
In still another embodiment the invention is a compound selected from the group consisting of:

GA1



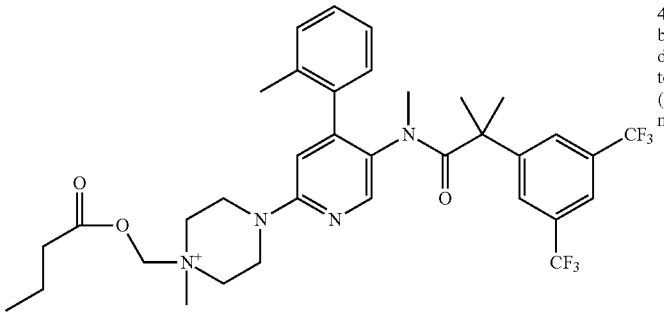
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphoncoxy)methyl) piperazin-1-ium,

GA2



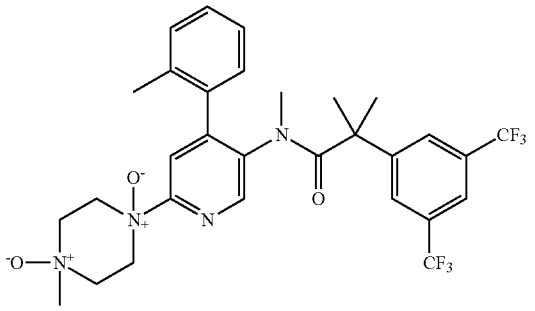
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,

GA3



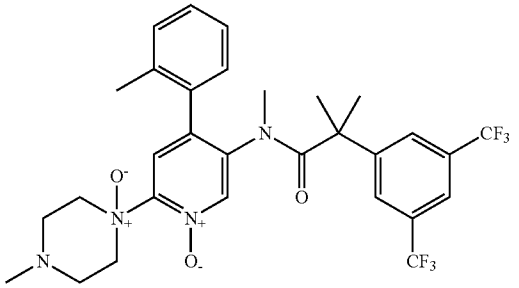
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,

GA4



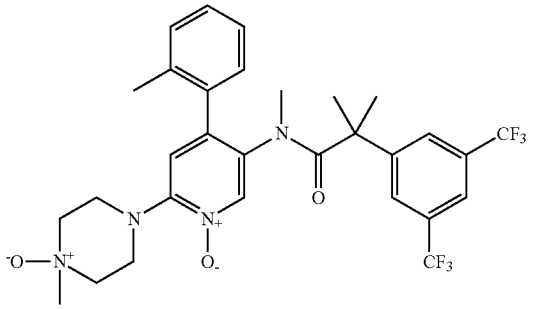
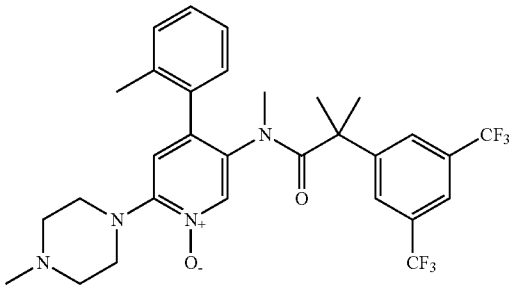
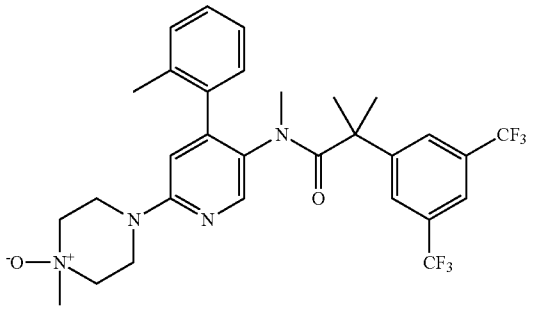
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

GA5



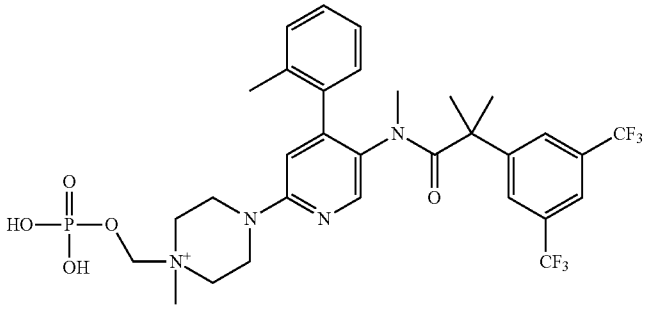
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

-continued

GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

or a pharmaceutically acceptable salt or adduct thereof.

In a further embodiment the invention is a compound of formula GA1,

formula GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphoncoxy)methyl) piperazin-1-ium

or a pharmaceutically acceptable salt or adduct thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** reproduces stability data for various salts of 4-(5-(2-(3,5-bis(trifluoro-methyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphor nooxy)methyl)piperazin-1-ium.

DETAILED DESCRIPTION

Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood

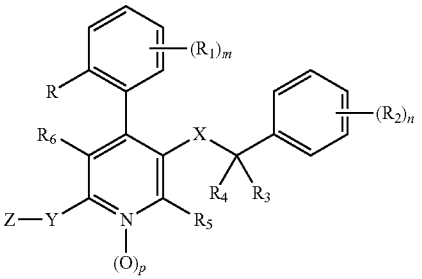
that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{1}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)N^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)2R^{102}$, —SR^{101}, $S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

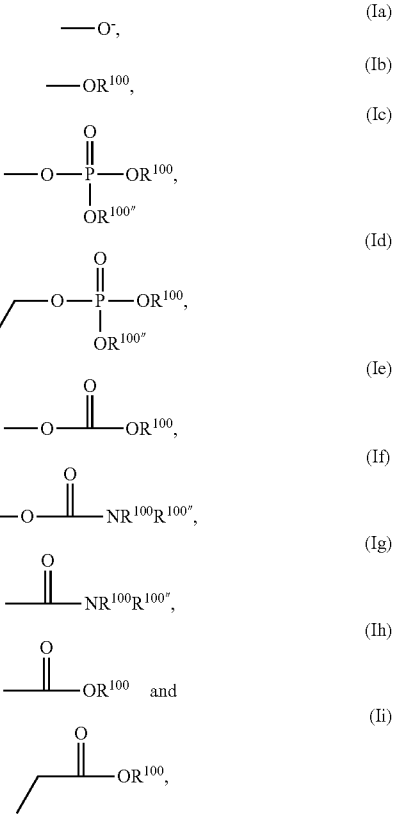
R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, $NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, $S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, $NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, $S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, $NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, $S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, $NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:



(Ia)

(Ib)

(Ic)

(Id)

(Ie)

(If)

(Ig)

(Ih) and

(Ii)

where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, $NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halo-

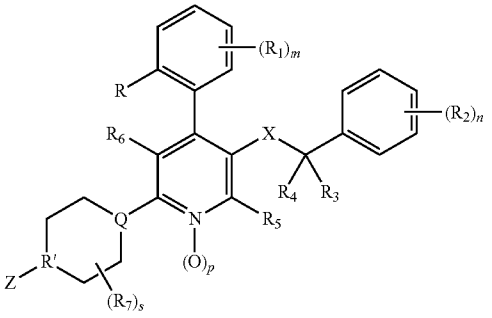
gen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is from 0 to 4; n is from 0 to 5; p is from 0 to 1; and with a proviso that if a non-pyridine N-Oxide ($N^{-}\rightarrow O^{+}$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein X is —$NR^{101}C(O)$. In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

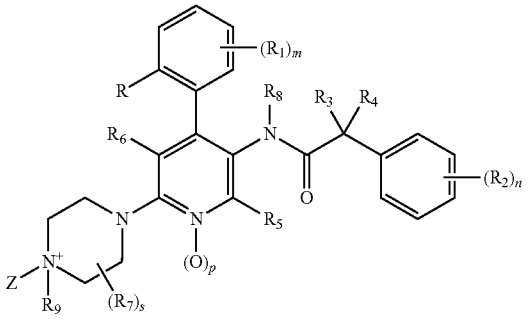
Formula (II)



where Q and R' are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

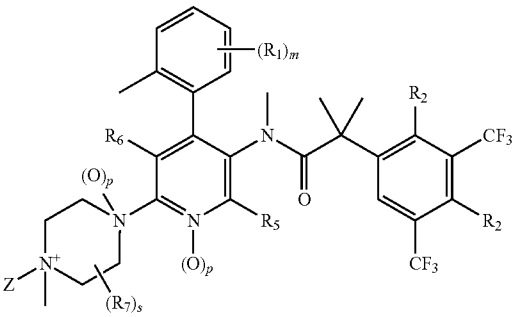
Formula (III)



where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

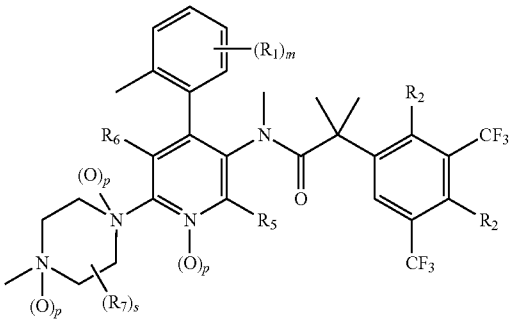
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

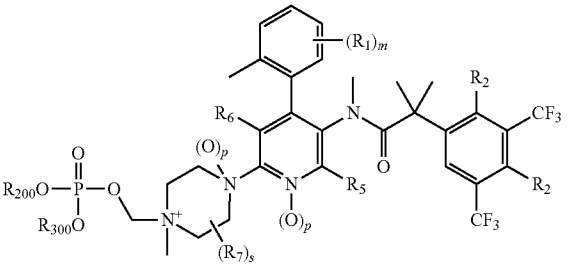
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (VI):

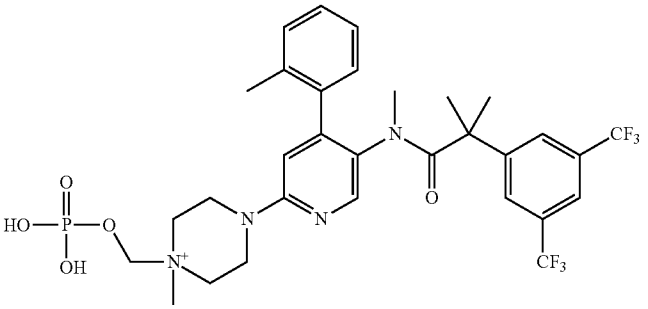
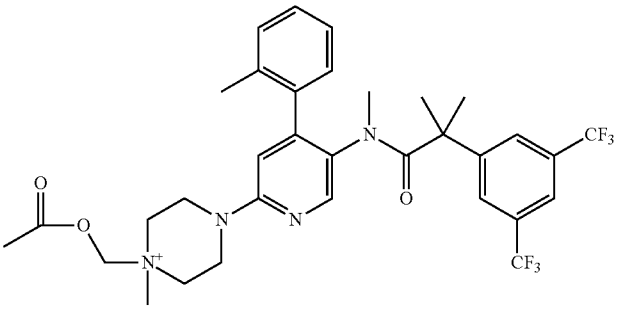
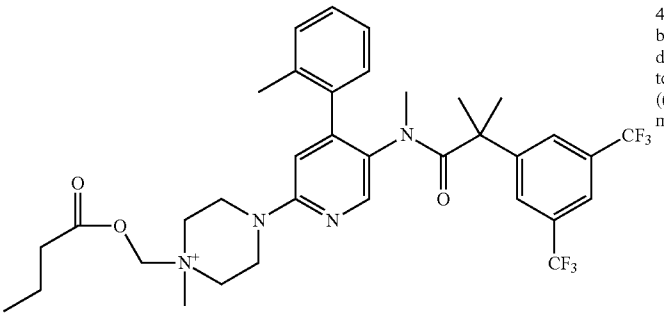
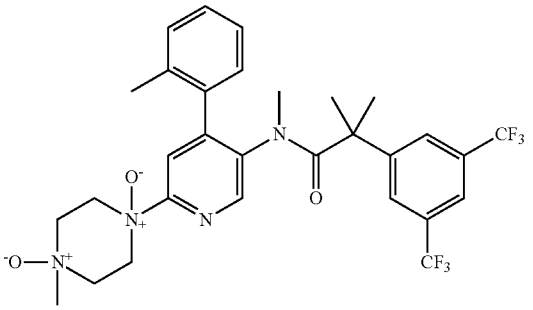
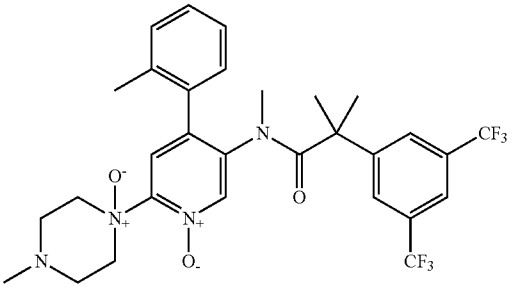
Formula (VI)



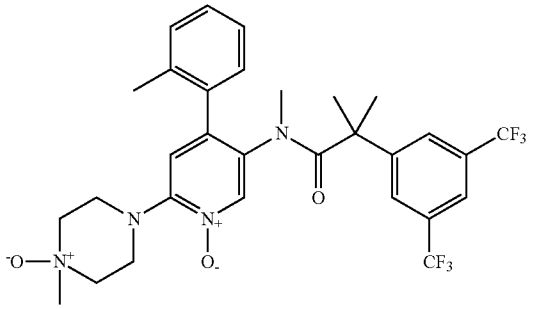
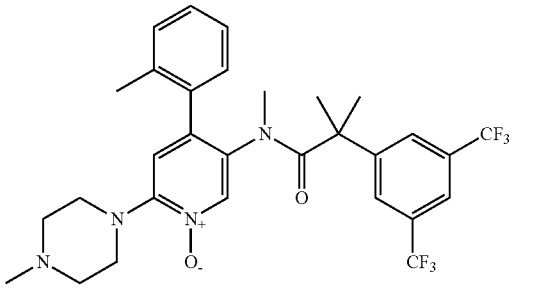
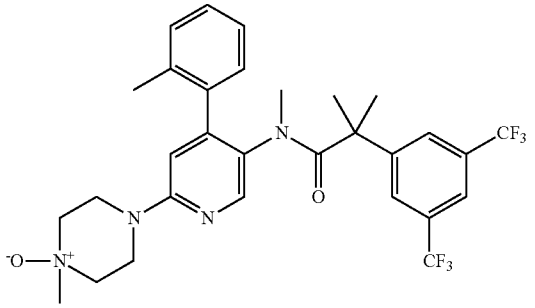
where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more inde-

pendent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

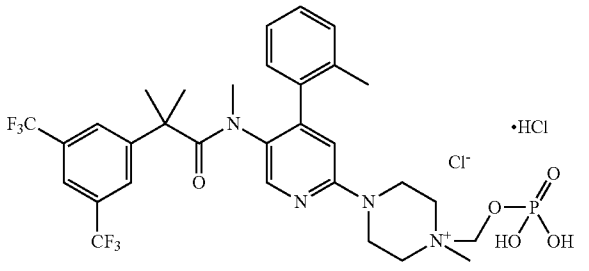
In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of:

GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphoncoxy)methyl) piperazin-1-ium,
GA2		1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,
GA3		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,
GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,
GA5		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

-continued

GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

A particular preferred compound is the chloride hydrochloride HCl salt of GA1 having the following chemical structure which, it has been found, is tremendously resistant to decoupling of the oxo-phosphonomethyl, and reversion of the active moiety to its parent state.



Salts and Adducts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced storage stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and

trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, (3-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

The disclosed compositions and compounds can be used in the form of adducts derived by formation of Lewis pairs, covalently linked adducts e.g. between N atoms and carbonyl-containing reactants, hydrates and alcoholates, host-guest adducts containing molecular species not bonded or associated with the medicinal compound, and other clathrates.

Depending on the particular compound, an adduct of the compound can be advantageous due to one or more of the adduct's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, an adduct of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where an adduct is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the adduct preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable adduct" refers to an adduct prepared by combining a compound, such as the disclosed compounds, with a gas, water, solvent, Lewis base, carbonyl-containing molecule, or guest molecule that is generally considered suitable for human consumption. Pharmaceutically acceptable addition species are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the adducts of the disclosed compounds are non-toxic "pharmaceutically acceptable adducts." Adducts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic adducts of the disclosed compounds which are generally prepared by reacting a compound of the invention with a suitable organic or inorganic addition species.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, include those derived from Lewis bases such as boric acid, aluminum hydroxide, organic sulfoxides, organic sulfones, organic sulfonium salts, H_3PO_3, siloxanes, and other Lewis bases.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from covalent bonding between an oxygen, nitrogen or sulfur atom of the compound and carbon dioxide, low alkyl aldehyde or ketone, vanillin, amino acid, or a nucleic acid.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from inclusion of an unbonded gas such as dioxygen, dinitrogen, carbon dioxide, nitrous oxide, ethyl ether, or other gas, contained within but not bonded to a crystalline or amorphous phase of the compound.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from association of a molecule of the compound with water, a pharmaceutically acceptable lower alkyl alcohol, or another pharmaceutically acceptable solvent that is associated in a molecular ratio with the compound.

In one embodiment the adduct is optionally a clathrate.

General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

The invention further provides methods for making suitable prodrugs of the 4-phenyl-pyridine derivatives. In one embodiment the invention provides a one-step, acid-free

synthesis for functionalizing tertiary amines by reaction with chloromethyl dialkyl phosphate esters to create (phosphooxy)methyl prodrugs that are substrates for phosphatase enzymes. By contrast the prior art had required multiple synthetic steps for comparable reactions, including requiring the use of proton scavengers during initial reaction and requiring strong acid to deprotect the phosphate group in another step. In another embodiment the invention provides methods for making chloromethyl dialkyl phosphate esters having suitable purity and economy, because the quality of phosphate ester compositions from commercial sources is too low to provide acceptable yields for reactions according to the invention. In an additional embodiment the invention provides a method to stabilize the (phosphooxy)methyl prodrugs according to the invention by combination with two equivalents of hydrochloric acid, because whereas the prior art preferred the use of dibasic salts of (phosphooxy) methyl substituents for quaternary ammonium salts in prodrugs, the present invention had found that such salts are unstable and reform the underlying drug during storage.

Definition of Terms

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms. In one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y—," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X-Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8

atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile") —CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The term "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula —$NH(CH_3)$), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to =O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to =S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxido" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane, thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term

"heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2—. The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2—. The term "methylenoxy" refers to the group —CH_2—O—. The term "methylenethioxy" refers to the group —CH_2—S—. The term "methylenamino" refers to the group —CH_2—N(H)—. The term "ethylenoxy" refers to the group —CH_2—CH_2—O—. The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule. If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active compounds and compositions, for example, can be administered orally, rectally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft

capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water).

Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution.

Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

In some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be

practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide ≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg. orally on day 1, followed by 8 mg. orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously administered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-day course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said 5-HT_3 antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg, or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 mL.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodi-

ment, the netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease. In some other forms, disclosed are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

More Definitions of Terms

1. A, an, the

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes not only single carriers but also mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. In order to more fully document the state of the art to which this invention pertains, the disclosures of these publications are to be considered as being referenced individually, specifically and in their entireties for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

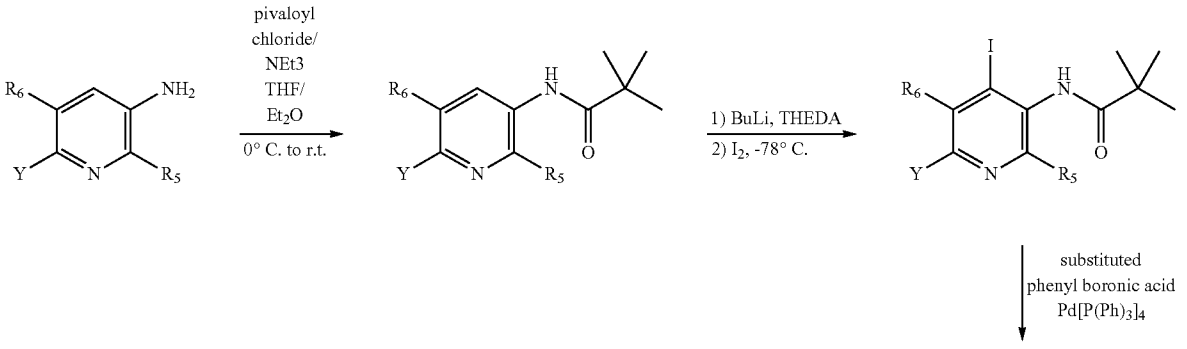
Example 1

Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

General Scheme of Preparing Compounds of Formula (I)

Scheme 1



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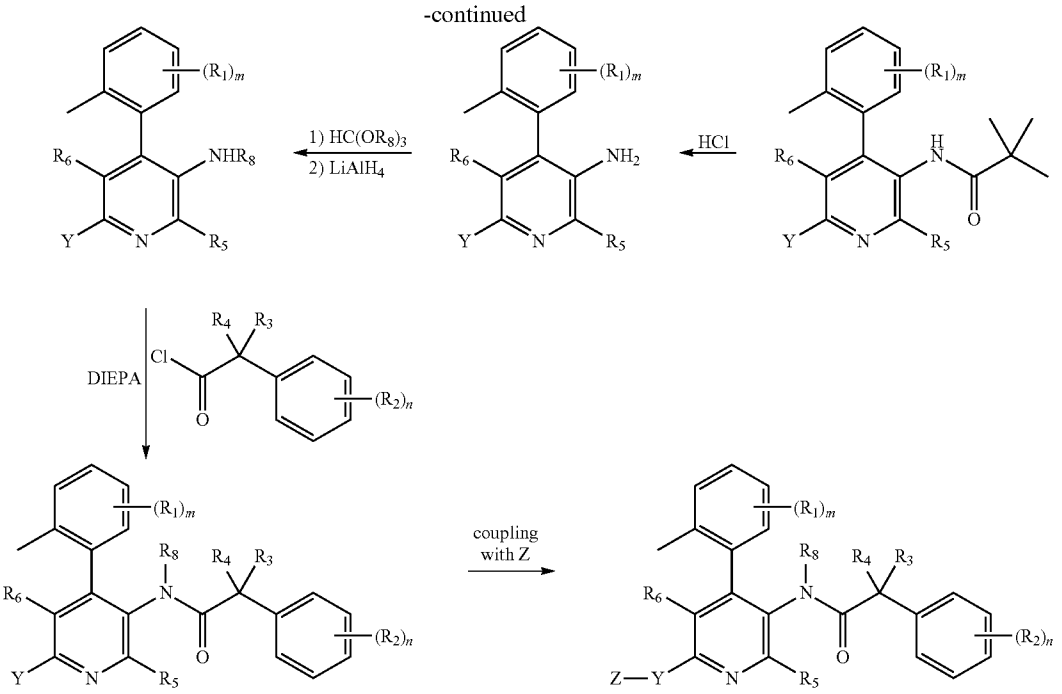
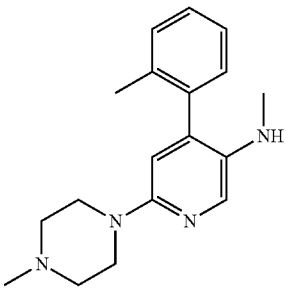


Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, which are referenced individually, specifically and in their entireties for the material contained in them that is relevant to the preparation of intermediate I.

Synthesis of methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THF were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolyl-magnesium chloride solution (1M in THF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THF removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent: ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution. The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THF were added 3.1 ml (42.0 mMol) thionylchloride and 143.mu.l (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0° C. After 30 minutes at 0° C., THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as a beige crystalline foam. MS (ISP): 247 ($M+H^+$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamide in 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam. MS (ISP): 311 ($M+H^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol 4:1) to yield 100 mg (70%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 ($M+H^+$, 100), 226 (42).

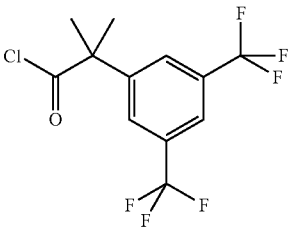
Step 5:

2.15 ml (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH=8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam. MS (ISP): 341 ($M+H^+$, 100), 284 (35).

Step 6:

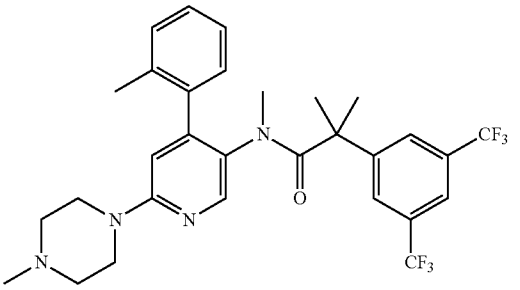
A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-Al® (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 ($M+H^+$, 100).

Synthesis of 2-(3,5-bis-Trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution was rotary evaporated to dryness. 9 ml Toluene were added and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, $3H_{arom}$); 1.77 (s, 6H, $2CH_3$).

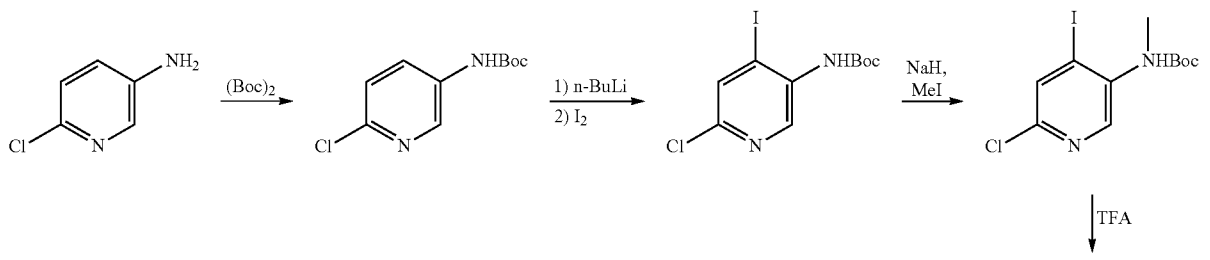
Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)



A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol)2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide as white crystals. M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2



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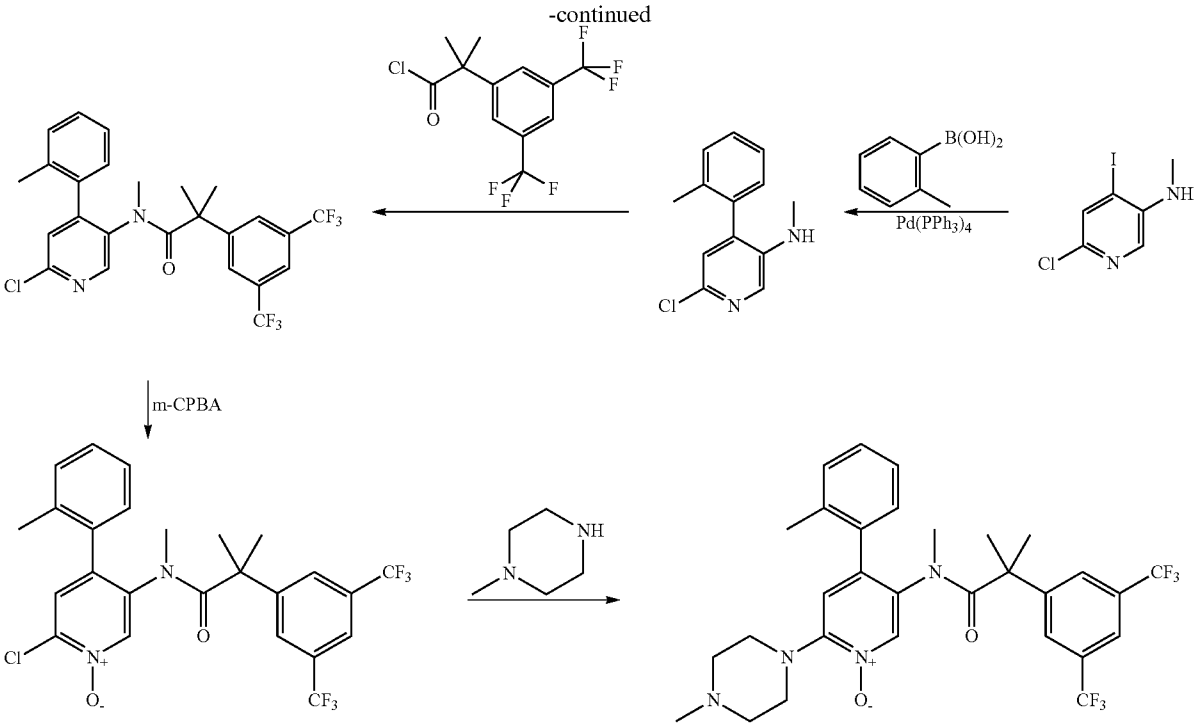


Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl (6-chloropyridin-3-yl) carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl (6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THF was added n-BuLi (600 mL, 1.5 mol) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THF was added. Then the solution was stirred at −78° C. for 4 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl (6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 mL of anhydrous THF was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THF was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl (6-chloro-4-iodopyridin-3-yl)(methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 mL of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol). The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under N_2 atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N, 2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropana-

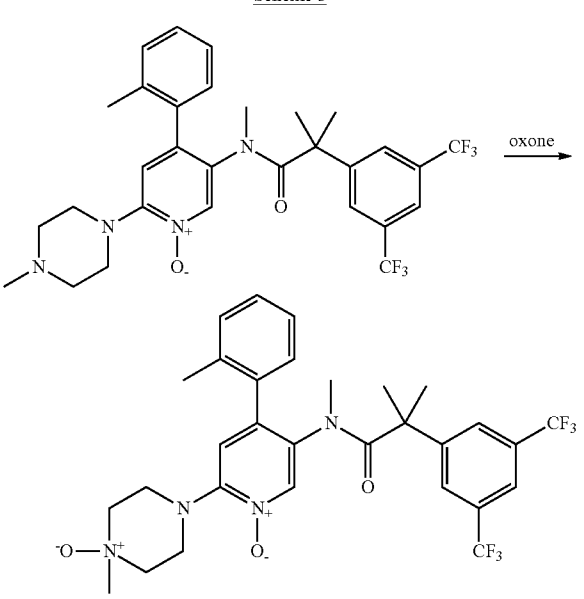
mide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature. 1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N, 2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45-1.20 (m, 6H).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide

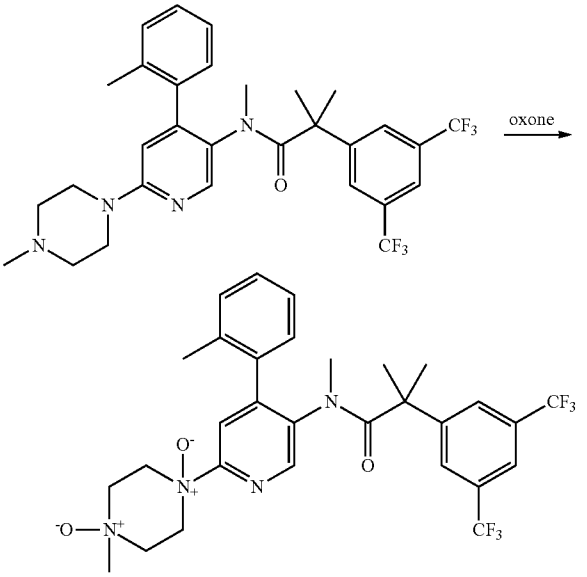
Scheme 3



To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N, 2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 mL of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for 4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N, 2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37-7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 2H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

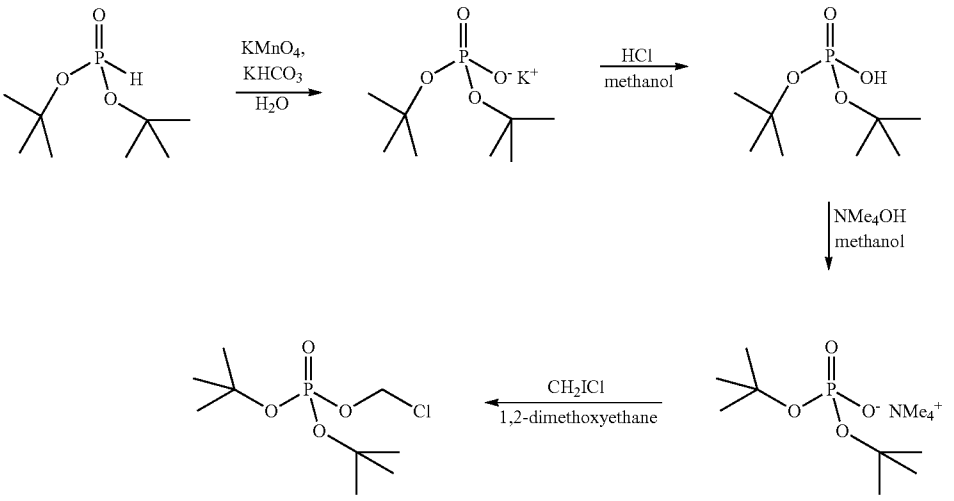
Scheme 4



To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N, 2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (3.38 g, 40.3 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR (CDCl3, 400 MHz, at 333K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26-7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

Synthesis (A) of di-tert-butyl (chloromethyl) phosphate

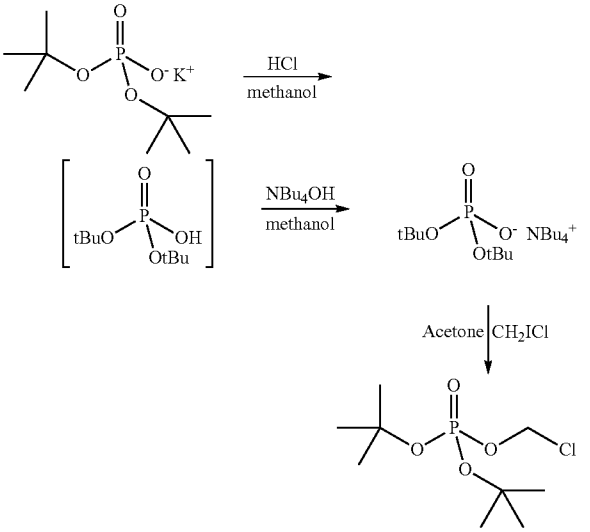
Scheme 5



Di-tert-butyl phosphite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time. The reaction as then allowed to continue at room temperature for an additional half hour. Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the crude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloriodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium without further purifications (60% yield): ^{1H}NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ-11.3 (s, 1 P).

Synthesis (B) of di-tert-butyl (chloromethyl) phosphate

Scheme 5A

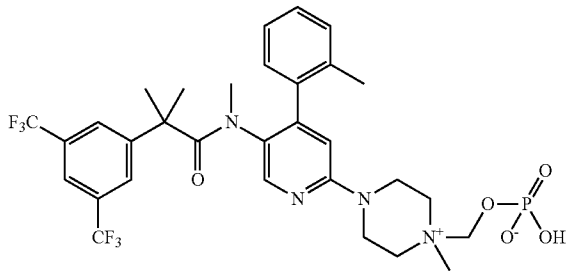


Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) is dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetrabuthylammonium hydroxide 1 M in methanol (20.14 mmole) while keeping the reaction cooled at 0° C. with efficient stirring. The resulting clear solution is placed under reduced pressure to give the intermediate product. The tetrabuthylammonium di-tert-butyl-

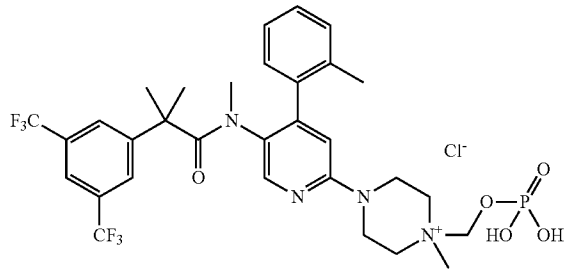
phosphate dissolved in acetone is then added dropwise to 53.3 grams of chloroiodomethane (302.1 mmole) and stirred at 40° C. for 1-2 hours. The solvent and excess of chloroiodomethane are distilled off, the reaction mass suspended in TBME and then filtered. The filtrate is washed by a saturated solution of sodium bicarbonate and water and then placed under reduced pressure to substitute the solvent by acetone, i.e., to remove the solvent after which it is replaced with acetone. The chloromethyl di-tert-butyl phosphate 7-20% in acetone is used in the next step without further purifications (70-80% yield): ^{1}H-NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ-11.3 (s, 1P).

Stability studies of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium salts

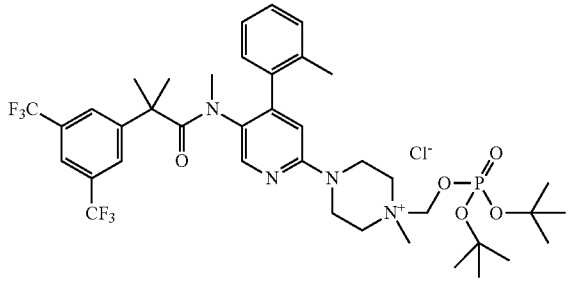
In order to further improve the stability and solubility of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium, a variety of its derivative salts were synthesized and tested. Their synthesis employed either a) neutralization of the dried diacid phosphate species and its corresponding base salts or b) a direct acid deprotection starting from the dried di(tert-butyl)-protected phosphate species. Neutralization was performed with L-histidine, magnesium salt, N-methyl-D-glucamine (dimeglumine), and L-lysine. Both procedures were tried in the synthesis of citric derivatives whereas with other acids the direct deprotection reaction was used. The figures below show the most relevant structures.



Parent acid species

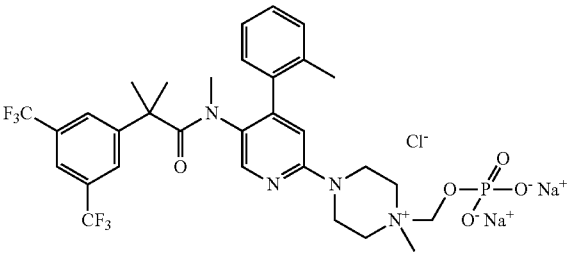


Diacid phosphate species

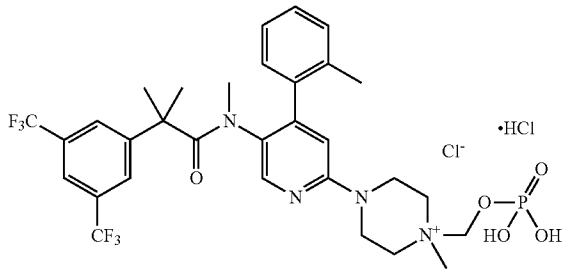


Protected phosphate species

-continued



Dibasic phosphate species



Chloride hydrochloride species

When the parent acid species was not stored in dry condition it was found to undergo over 8% degradation in the first week and over 65% degradation in the first six months. When the dried parent acid species was held at 30° C. in air it underwent 0.05% degradation in the first 7 days and at total of 7.03% degradation in six months. When the dried parent acid species was held under argon at room temperature it underwent up to 0.13% degradation in the first 7 days but then was essentially stable for six months. Results for various derivative salts are shown in Table 1 below.

TABLE 1

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	L-Histidine, 2 eq.	26.6%	95.94%	Degradation: +0.70% in 6 days (in air) 0.46% in 6 days (in argon)
MeOH	$Mg(OH)_2$, 2 eq.	48.6%	94.11%	Degradation: +0.81% in 6 days (in air) +0.29% in 6 days (in argon)
MeOH + DCM, 1:1	Citric acid, 2 eq.	N.A.	94.40%	From protected species.
MeOH	1. HCl dioxane, 4 eq. 2. $Ca(OH)_2$	>90%	94.50%	From protected species.
MeOH	H_3PO_4, 85%, 2 eq.	>90%	98.81%	From protected species and retains 0.39% of that species.
MeOH	HBr, 48%, 4 eq.	84.6%	96.11%	From protected species. Product degrades rapidly.
MeOH + DCM, 1:4	CH_3SO_3H	N.A.	61.54%	From protected species. Product NOT stable: contains 32.45% decomposition species.
MeOH	NaH_2PO_4, 4 eq.	N.A.	n.d.	Only 1.27 of parent species formed. Poor reaction.

TABLE 1-continued

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	N-methyl-D-glucamine (Meglumine), 2 eq.	N.A.	96.88%	Degradation: +0.87% in 6 days (in air) +1.52% in 11 days (in argon)
MeOH	N-methyl-D-glucamine (Meglumine), 1 eq.	>99%	97.42%	Degradation: +0.77% in 6 days (in air) +0.83% in 7 days (in argon)
MeOH + DCM, 5:2	1. NaOH, 3 eq 2. Citric acid, 1 eq.	96.5%	97.49%	Degradation: +0.09% in 2 days (in argon) +0.59% in 89 days (in argon)
MeOH + DCM, 5:2	1. NaOH,3 eq. 2. Fumaric acid, 1 eq.	93.8%	97.46%	Degradation: +1.95% in 14 days (in air) +1.80% in 12 days (in argon)
MeOH	L-lysine, 1 eq.	>99%	97.62%	Degradation: +0.69% in 14 days (in air) +0.48% in 12 days (in argon)

A more comprehensive showing of stability results is given in FIG. **1**, where the horizontal axis represents number of days of testing and the vertical axis represents the mass percent of degradation. Alphabetical letters are used to denote data points on the graph that correspond to degradation percentage values over time for respective salts of the same parent compound as just described above and in Table 2 below. The drawn lines correspond to general trends over periods of days for the benchmark salt (the disodium salt) and for the few salts that manifested more desirable results than the disodium salt.

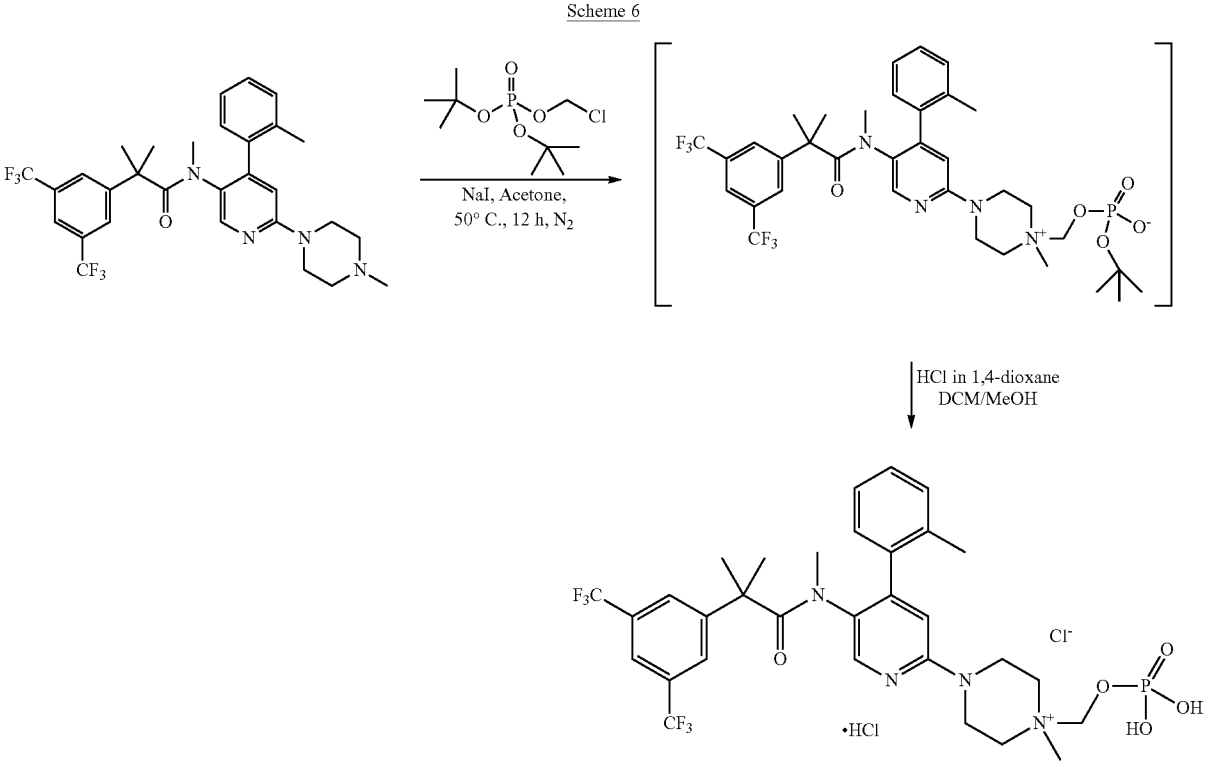
TABLE 2

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
a	2 Dimeglumine	Air
b	2 Dimeglumine	Argon
c	Dimeglumine	Air
d	Dimeglumine	Argon
e	Lysine	Air
f	Lysine	Argon
g	Fumarate	Air
h	Fumarate	Argon
i	Citrate	Air
j	Citrate	Argon
k	Bromide	Air
l	Bromide	Argon
m	Mesylate	Nitrogen
n	Phosphate	Air
o	Phosphate	Argon
p	Citrate	Nitrogen
q	Calcium	Air
r	Calcium	Argon
s	Chloride hydrochloride, anhydrous	Air
t	Chloride hydrochloride, anhydrous	Argon
u	Disodium salt	Air
v	Histidine	Air
w	Histidine	Argon
x	Magnesium	Air
y	Magnesium	Argon

Synthesis (A) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

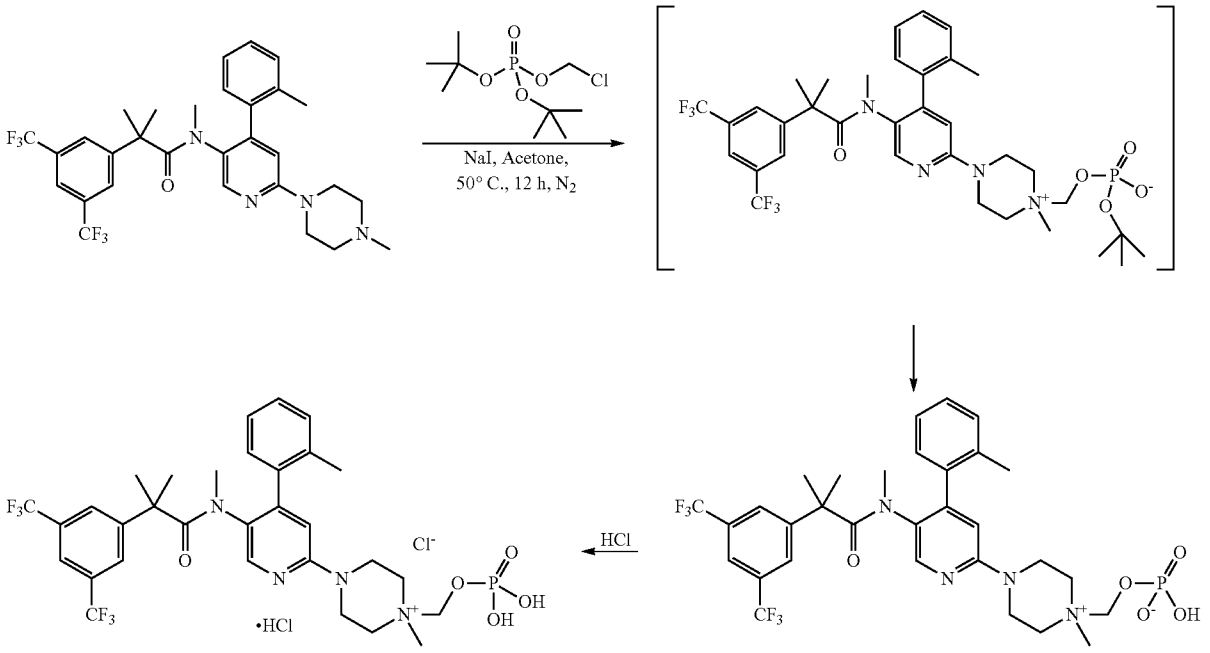
Scheme 6



The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile. 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphtalene and 46.6 g (80.54 mmole) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropylether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropylether/acetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-7.10 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m. 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ-5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N, 2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride as white solid (Yield: 88-93%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ-2.81 (t, 1P, J_{PH}=7.9 Hz).

Synthesis (B) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

Scheme 6A



To the solution of chloromethyl di-tert-butyl phosphate in Acetone (22.1 g from a 10% solution, 85.58 mmole), 15.5 g (103.24 mmole) of sodium iodide and 33.0 g (57.00 mmole) of netupitant were added and the solution heated at 50° C. for at 6-16 h. The precipitated salts were filtered off, the acetone distilled under reduced pressure and the crude product dissolved in 43.0 g of methanol and 43.0 g 1,4-dioxane. 12.6 g of HCl 4M in dioxane (113.85 mmole) were added, and then methanol is distilled off at 40° C. under reduced pressure. The solution is cooled at 5° C. and stirred at 5° C. for at least 2 h at 5° C. The product was isolated by filtration, purified by additional slurry in acetone (238 g), and filtered and washed with acetone (47 g) and pentane (2×72 g).

The product was finally dried under reduced pressure at 60° C. to afford 22-30 g of white-yellowish solid (Yield: 50-70%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m,

2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ-2.81 (t, 1P, J_{PH}=7.9 Hz).

It is to be understood that the product shown in Scheme 6A is illustrative, being just one of several permutations in which the acidic protons bond to various atoms in an equilibrium.

For instance depiction of other permutations would show a proton bound to one or more of the N atoms while one or more of the O atoms bound to the P atom would bear an anionic charge.

The invention comprises all of the molecular species within that equilibrium and the product shown in the figure is intended to represent all of them in a generic fashion.

7. Evaluation of Representative Compounds of Formula (I)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 3 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE 3

Chemical Stability and Solubility of Representative Compounds

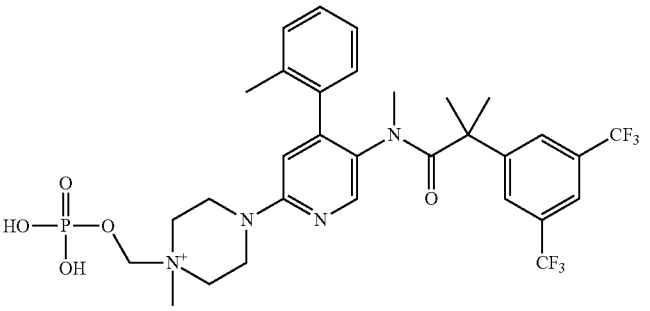
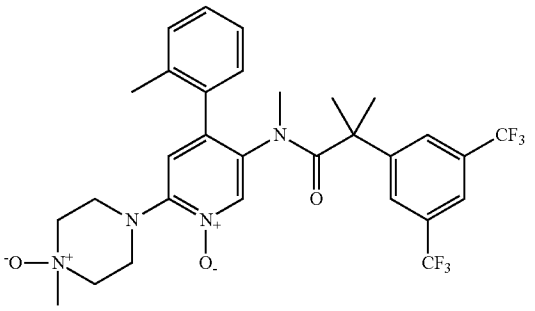
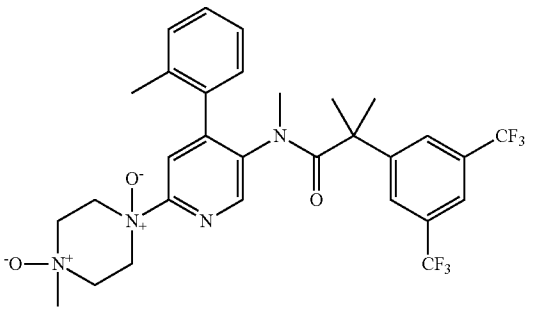
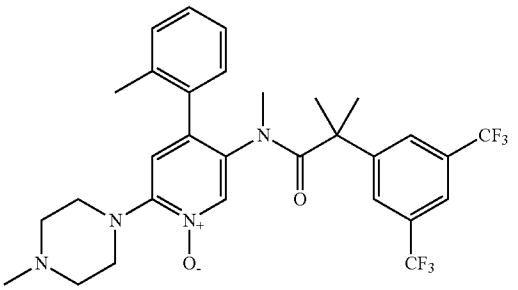
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1		medium	10-15 mg/ml
2		high	>10 mg/ml
3		high	>10 mg/ml
4		medium	~0.6 mg/ml

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

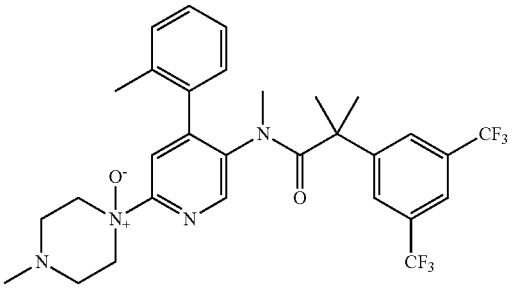
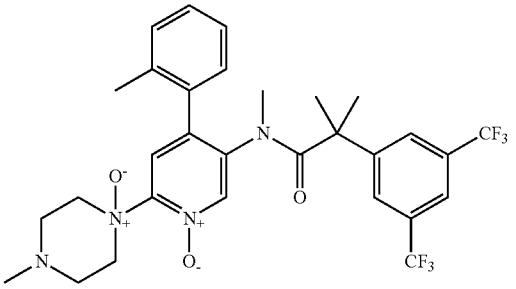
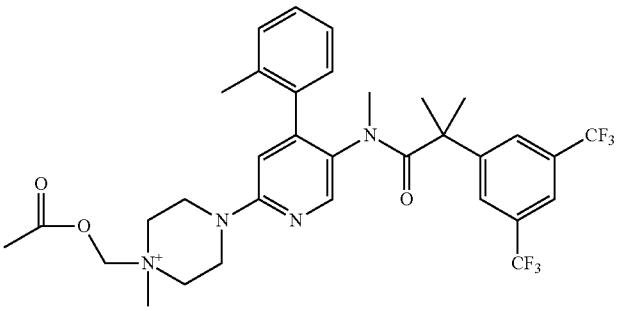
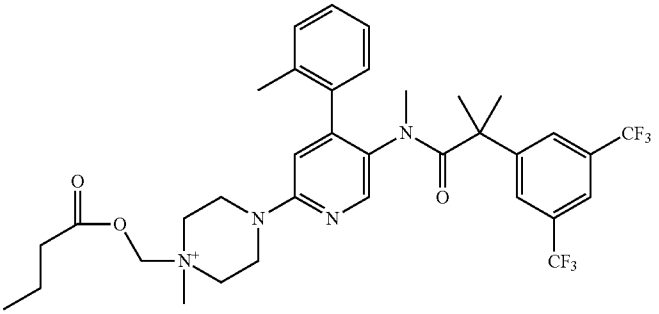
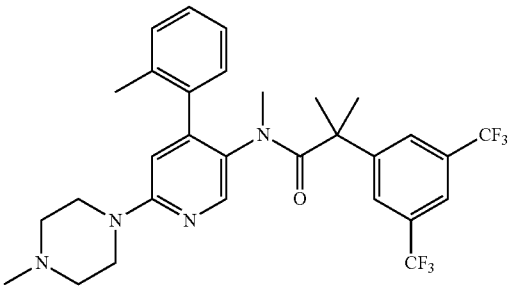
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
5*		medium	~1 mg/ml
6		low	N/A
7		low	insoluble
8		Low	insoluble

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
9*			0.25

*Reference Compound

ii. Local Tolerance

In contrast to netupitant (compound no. 9 in the above table), seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

There were minimal signs of inflammation at injection site and there was little edema;

No later stage thrombus was found in any animal studied;

Severity of inflammation was similar in compound and vehicle-treated animals;

No tissue necrosis was observed in any of the tails; and

The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 3), as compared to a reference compound—netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a dose volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Before administration, rats were fasted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pre-dose and at 0.05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO: Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solubility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (IV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, 15 and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC.

MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 3, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 4:

TABLE 4

Comparative Bioequivalence Studies of Netupitant and Related Compounds

	IV			PO
	Compound 1	Compound 2	Compound 3	Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng · min/ml)	315627	88732	192730	307285
Bioequivalence (%)	103	29	63	

*Reference Compound

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby referenced individually and specifically for the material contained in them that is discussed in the sentence in which the reference is relied upon. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method for preventing acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy, comprising intravenously administering to the human patient, prior to the chemotherapy, a solution comprising a therapeutically effective amount of the chloride hydrochloride salt of fosnetupitant and a therapeutically effective amount of palonosetron hydrochloride, in combination with a therapeutically effective amount of dexamethasone.

2. The method of claim **1**, wherein the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule and the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base.

3. The method of claim **1**, wherein the solution has a concentration of from 2 mg/mL to 5 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule.

4. The method of claim **1**, wherein the solution has a concentration of from 5 mg/mL to 15 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule.

5. The method of claim **1**, wherein the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule, the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base, and the solution has a concentration of from 2 mg/mL to 5 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule.

6. The method of claim **1**, wherein the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule, the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base, and the solution has a concentration of from 5 mg/mL to 15 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule.

7. The method of claim **1**, wherein the therapeutically effective amount of dexamethasone comprises 12 mg administered orally on day 1, 8 mg administered orally on day 2, 8 mg administered orally on day 3 and 8 mg administered orally on day 4.

8. The method of claim **1**, wherein the method consists of intravenously administering to the human patient, prior to the chemotherapy, a solution comprising a therapeutically effective amount of the chloride hydrochloride salt of fosnetupitant and a therapeutically effective amount of palonosetron hydrochloride, in combination with a therapeutically effective amount of dexamethasone.

9. The method of claim **1**, wherein the fosnetupitant independently prevents acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy.

10. A method for preventing acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy, comprising intravenously administering to the human patient, prior to the chemotherapy, a solution comprising a therapeutically effective amount of the chloride hydrochloride salt of fosnetupitant and a therapeutically effective amount of palonosetron hydrochloride, in combination with a therapeutically effective amount of dexamethasone, wherein:

(a) the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule;

(b) the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base; and

(c) the solution has a concentration of from 2 mg/mL to 5 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule.

11. A method for preventing acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy, comprising intravenously administering to the human patient, prior to the chemotherapy, a solution comprising a therapeutically effective amount of the chloride hydrochloride salt of fosnetupitant and a therapeutically effective amount of palonosetron hydrochloride, in combination with a therapeutically effective amount of dexamethasone, wherein:

(a) the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule;

(b) the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base; and

(c) the solution has a concentration of from 5 mg/mL to 15 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule.

12. A method for preventing acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy, consisting of intravenously administering to the human patient, prior to the chemotherapy, a solution comprising a therapeutically effective amount of the chloride hydrochloride salt of fosnetupitant and a therapeutically effective amount of palonosetron hydrochloride, in combination with a therapeutically effective amount of dexamethasone, wherein:

(a) the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule;

(b) the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base;

(c) the solution has a concentration of from 2 mg/mL to 5 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule; and

(d) the therapeutically effective amount of dexamethasone comprises 12 mg administered orally on day 1, 8 mg administered orally on day 2, 8 mg administered orally on day 3 and 8 mg administered orally on day 4.

13. A method for preventing acute and delayed nausea and vomiting in a human patient receiving highly emetogenic cancer chemotherapy, consisting of intravenously administering to the human patient, prior to the chemotherapy, a solution comprising a therapeutically effective amount of the chloride hydrochloride salt of fosnetupitant and a therapeutically effective amount of palonosetron hydrochloride, in combination with a therapeutically effective amount of dexamethasone, wherein:

(a) the chloride hydrochloride salt of fosnetupitant is administered in an amount of from 150 mg to 200 mg based on the netupitant portion of the molecule;

(b) the palonosetron hydrochloride is administered in an amount of 0.25 mg based on the weight of the free base;

(c) the solution has a concentration of from 5 mg/mL to 15 mg/mL of the chloride hydrochloride salt of fosnetupitant based on the weight of the netupitant portion of the molecule; and

(d) the therapeutically effective amount of dexamethasone comprises 12 mg administered orally on day 1, 8 mg administered orally on day 2, 8 mg administered orally on day 3 and 8 mg administered orally on day 4.

* * * * *

Exhibit G

US010624911B2

(12) **United States Patent**
Venturini et al.

(10) **Patent No.: US 10,624,911 B2**
(45) **Date of Patent: Apr. 21, 2020**

(54) **PHYSIOLOGICALLY BALANCED INJECTABLE FORMULATIONS OF FOSNETUPITANT**

(71) Applicant: **HELSINN HEALTHCARE SA**, Lugano/Pazzallo (CH)

(72) Inventors: **Alessio Venturini**, Varese (IT); **Roberta Cannella**, Varese (IT)

(73) Assignee: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/611,785**

(22) Filed: **Jun. 2, 2017**

(65) **Prior Publication Data**

US 2017/0348335 A1 Dec. 7, 2017

Related U.S. Application Data

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(51) **Int. Cl.**

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A61K 31/496	(2006.01)
A61K 31/675	(2006.01)
A61K 9/00	(2006.01)
A61K 9/08	(2006.01)
A61K 9/19	(2006.01)
A61K 47/02	(2006.01)
A61K 47/26	(2006.01)
A61K 47/18	(2017.01)
A61P 1/08	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/675*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 9/19*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 47/02*** (2013.01); ***A61K 47/183*** (2013.01); ***A61K 47/26*** (2013.01); ***A61P 1/08*** (2018.01)

(58) **Field of Classification Search**

CPC .. A61K 31/473; A61K 31/496; A61K 31/675; A61K 9/0019; A61K 9/08; A61K 9/19; A61K 47/02; A61K 47/183; A61K 47/26; A61P 1/08

See application file for complete search history.

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Primary Examiner — Sarah Pihonak
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan

(57) **ABSTRACT**

Injectable dosages and formulations of fosnetupitant and pharmaceutically acceptable salts thereof are provided that are efficacious, chemically stable and physiologically balanced for safety and efficacy.

21 Claims, 2 Drawing Sheets

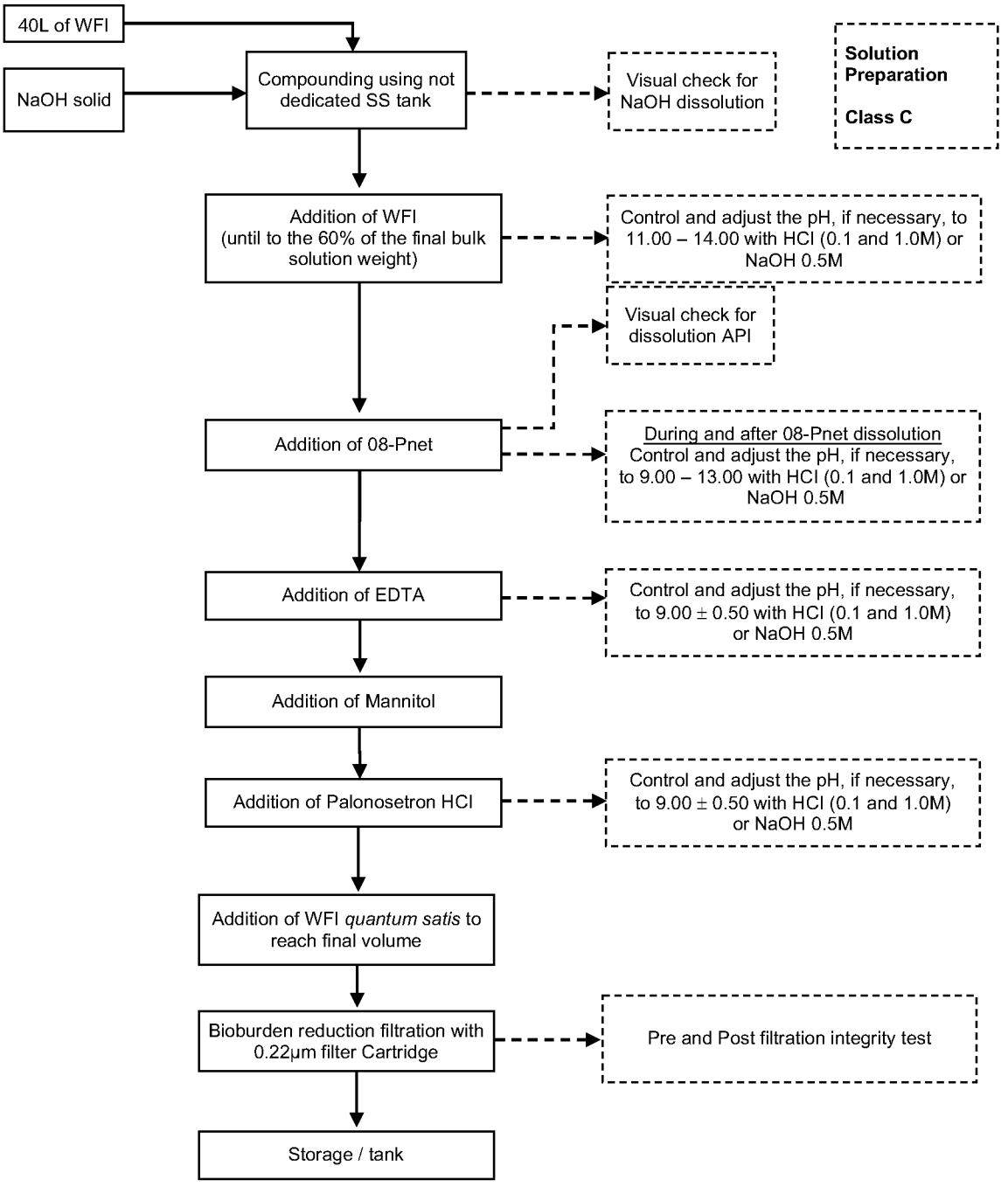

40L of WFI
NaOH solid
Compounding using not dedicated SS tank
Visual check for NaOH dissolution
Solution Preparation
Class C
Addition of WFI (until to the 60% of the final bulk solution weight)
Control and adjust the pH, if necessary, to 11.00 – 14.00 with HCl (0.1 and 1.0M) or NaOH 0.5M
Visual check for dissolution API
Addition of 08-Pnet
During and after 08-Pnet dissolution Control and adjust the pH, if necessary, to 9.00 – 13.00 with HCl (0.1 and 1.0M) or NaOH 0.5M
Addition of EDTA
Control and adjust the pH, if necessary, to 9.00 ± 0.50 with HCl (0.1 and 1.0M) or NaOH 0.5M
Addition of Mannitol
Addition of Palonosetron HCl
Control and adjust the pH, if necessary, to 9.00 ± 0.50 with HCl (0.1 and 1.0M) or NaOH 0.5M
Addition of WFI *quantum satis* to reach final volume
Bioburden reduction filtration with 0.22µm filter Cartridge
Pre and Post filtration integrity test
Storage / tank

Figure 1

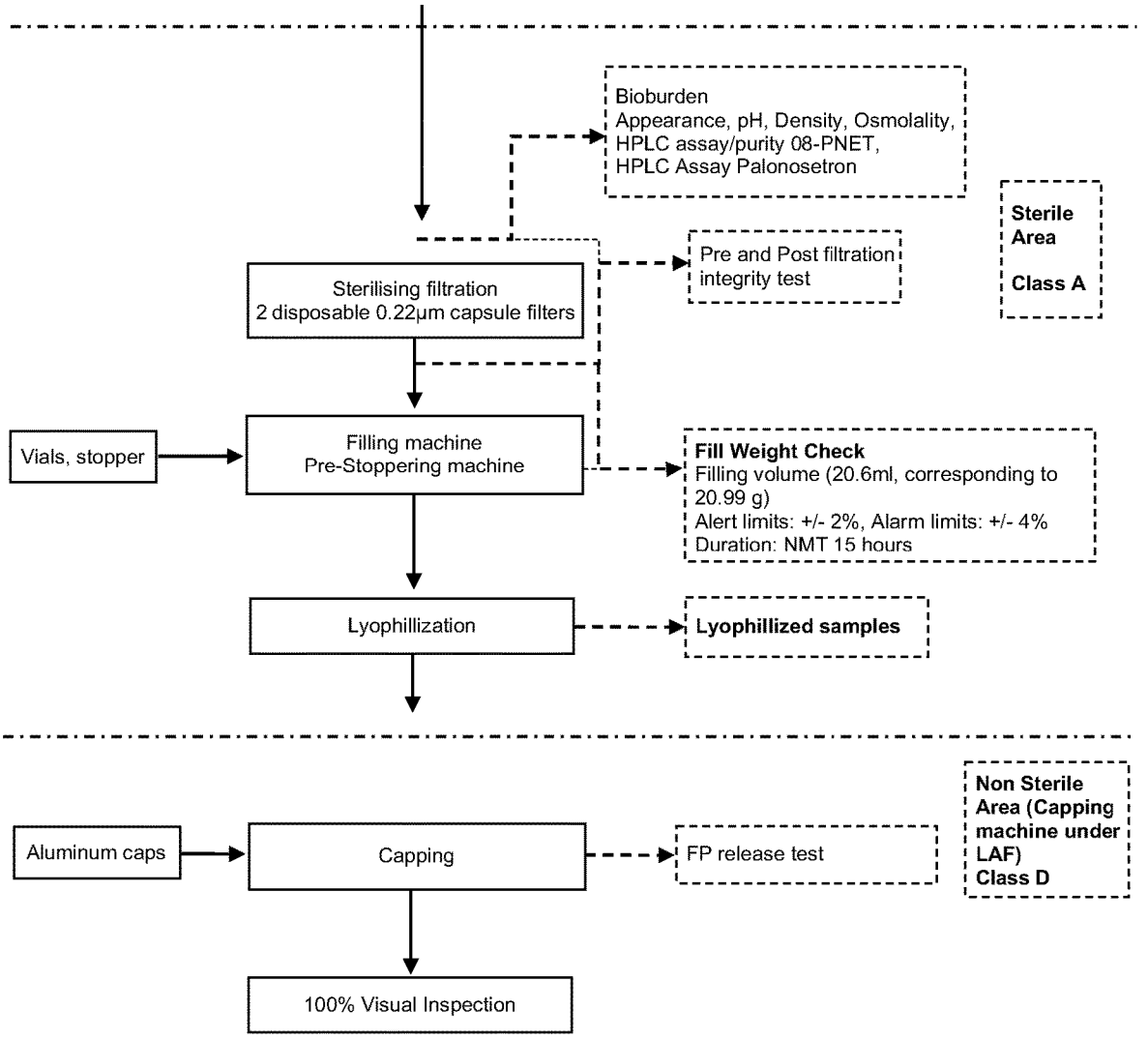

Bioburden
Appearance, pH, Density, Osmolality,
HPLC assay/purity 08-PNET,
HPLC Assay Palonosetron
Sterile Area
Class A
Pre and Post filtration integrity test
Sterilising filtration
2 disposable 0.22µm capsule filters
Vials, stopper
Filling machine
Pre-Stoppering machine
Fill Weight Check
Filling volume (20.6ml, corresponding to 20.99 g)
Alert limits: +/- 2%, Alarm limits: +/- 4%
Duration: NMT 15 hours
Lyophillization
Lyophillized samples
Aluminum caps
Capping
FP release test
Non Sterile Area (Capping machine under LAF)
Class D
100% Visual Inspection

Figure 2

PHYSIOLOGICALLY BALANCED INJECTABLE FORMULATIONS OF FOSNETUPITANT

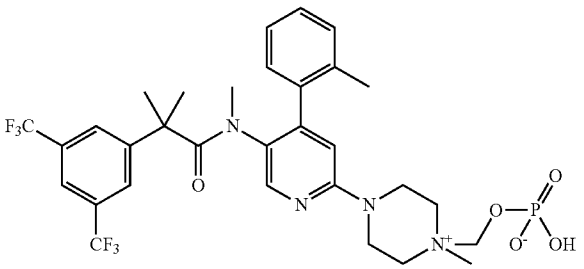
FIELD OF INVENTION

The present invention relates to lyophilized and liquid injectable dosages and formulations of fosnetupitant and pharmaceutically acceptable salts thereof that are efficacious, chemically stable and physiologically balanced for safety and efficacy.

BACKGROUND OF INVENTION

Fosnetupitant is a neurokynin-1 ("NK-1") antagonist under development by Helsinn Healthcare SA, Lugano/Pazzallo Switzerland, for the treatment of chemotherapy induced nausea and vomiting. The active moiety of fosnetupitant, netupitant, is approved in the United States as Akynzeo®, an orally administered capsule that contains 300 mg of netupitant and 0.5 mg palonosetron as palonosetron HCl.

Fosnetupitant is known chemically as 4-(5-(2-(3,5-bis (trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium. The compound has the following chemical structure in its acidic/free base form:



The molecular weight of the compound in its free base form is 688.6 g/mol. The molecular weight of the chloride hydrochloride salt is 761.53 g/mol.

A method of preparing fosnetupitant is described in WO 2013/082102. According to WO 2013/082102, the compound was developed partly to overcome injection site issues that occurred when its active moiety (netupitant) was administered as the free base. According to WO 2013/082102, "a single intravenous dose of fosnetupitant is intravenously administered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule." In preferred intravenous formulations, the fosnetupitant is reportedly present at a concentration of about 10 mg/mL, again based on the weight of the active moiety.

New intravenous doses and formulations of fosnetupitant are needed for use in the clinic and commercial distribution. However, formulation development is complicated by the degradation of fosnetupitant and some solubility issues. As reported in Table 1 of WO 2013/082102, degradation of the compound can be significant.

The development of fosnetupitant is also complicated by bioavailability issues associated with the parent molecule (netupitant). As reported in the FDA-approved prescribing information for Akynzeo®, "there was a greater than dose-proportional increase in the systemic exposure with the dose increase from 10 mg to 300 mg and a dose-proportional increase in systemic exposure with a dose increase from 300 mg to 450 mg."

A further problem arises in that fosnetupitant (although being more soluble than netupitant), remains a moderately soluble molecule which takes special additives such as surfactants (e.g. polyoxyethylenesorbitan monooleate, etc.) to maintain the product in solution during manufacturing, storage and/or reconstitution in water from solid forms; yet the use of these agents is preferably to be avoided as potentially harmful, in compliance with regulatory safety recommendations. In addition, the present inventors have unexpectedly found, during development studies leading to the present invention, that the solubility of fosnetupitant solutions varies irregularly and unpredictably as a function of small environmental changes (e.g. concentration, temperature, pH, presence of additives like buffers, chelating agents, etc.); the inventors also found that the solubility behavior of fosnetupitant is complicated by its spontaneous partial conversion into the lesser soluble active moiety (netupitant) and/or lesser soluble degradation products: the solubility of such products may respond to criteria different from those optimizing the solubility of fosnetupitant. The overall solubility of fosnetupitant is thus the result of an interplay of different solubilities of different components of the formulation.

Accordingly, it is an object of the invention to provide injection doses of fosnetupitant for the treatment of diseases mediated by the NK1 receptor, including nausea, emesis, and chemotherapy induced nausea and vomiting.

Another object of the present invention is to provide injectable formulations of fosnetupitant with improved stability, solubility, less degradation, and improved physiological tolerance.

Still another object is to provide methods of making injectable formulations of fosnetupitant, and methods of using such formulations in the treatment of diseases modulated by the NK-1 receptor.

Still further objects are to provide formulations that remain stable and soluble when reconstituted with traditional injection media such as glucose and saline.

Still further objects are to provide formulations that remain stable and soluble when formulated and/or stored as solutions; or when formulated and/or stored in solid form; or when reconstituted from solid form with traditional injection media such as glucose and saline.

Additional objects are to provide methods of manufacturing fosnetupitant formulations that protect the final formulation against degradation.

SUMMARY OF THE INVENTION

The inventors have made several important discoveries which enable for the first time lyophilized and liquid injectable formulations of fosnetupitant that are shelf stable and do not cause unwanted injection site reactions. By carefully balancing netupitant and fosnetupitant concentrations in the formulation, and selecting an appropriate pH or appropriate pH adjusting agents for the final solution, an elegant formulation is obtained that remains stable for prolonged periods of time, and does not cause injection site reactions.

Therefore, in a first principal embodiment the invention provides a pharmaceutically stable injectable formulation of fosnetupitant and netupitant at a balanced ratio, as a liquid solution or lyophilized powder, comprising: (a) from 95 to 99.99 weight parts fosnetupitant or a pharmaceutically acceptable salt thereof; and (b) from 0.01 to 5 weight parts

netupitant or a pharmaceutically acceptable salt thereof; and (c) pH adjusting means for maintaining said balanced ratio. When the formulation is in an aqueous liquid solution, at a fosnetupitant concentration of approximately 11.8 mg/ml (based on the weight of fosnetupitant free base), said fosnetupitant or pharmaceutically acceptable salt thereof is preferably completely dissolved in said formulation. The pH adjusting means can be characterized by the resulting pH (preferably 7 to 10 in the final formulation), or the agents used to adjust the pH (preferably hydrochloric acid as the acidifying agent and sodium hydroxide as the alkalizing agent).

In another principal embodiment, the invention provides an injectable liquid solution comprising: (a) from 2.3 to 30 mg/mL of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base (b) optionally, from 5 to 30 μg/mL of palonosetron or a pharmaceutically acceptable salt thereof, based on the weight of the free base; (c) sodium hydroxide; (d) disodium edetate; (e) optionally hydrochloric acid; (f) mannitol; and (g) water q.s.

In another principal embodiment, the invention provides an injectable lyophilized powder which, when reconstituted to a suitable volume, comprises (a) from 2.3 to 30 mg/mL of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base; (b) optionally, from 5 to 50 μg/mL of palonosetron or a pharmaceutically acceptable salt thereof, based on the weight of the free base; (c) sodium hydroxide; (d) disodium edetate; (e) optionally hydrochloric acid; and (f) mannitol.

Other embodiments provide a single unit dose injectable formulation of fosnetupitant (liquid or lyophilized powder) comprising approximately 235 mg of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base (corresponding to a 260 mg weight of the salt, in case of the chloride hydrochloride salt of fosnetupitant). Still further embodiments provide a method of treating emesis in a human subject in need thereof by administering an intravenous dose of approximately 235 mg of fosnetupitant, or a pharmaceutically acceptable salt thereof, based on the weight of the free base of fosnetupitant.

Still other embodiments provide methods of manufacturing the formulation to provide a stable, safe and effective formulation. Thus, in one embodiment the invention provides a method of manufacturing a liquid injectable formulation of fosnetupitant comprising: (a) admixing the chloride hydrochloride salt of fosnetupitant with sodium hydroxide in water at a basic pH to form a solution; (b) reducing the pH of the solution by the addition of one or more acidic pH adjusting agents; and (c) optionally admixing the solution with one or more pharmaceutically acceptable excipients. In a particularly preferred embodiment the one or more acidic pH adjusting agents comprises disodium edetate and/or hydrochloric acid.

Additional advantages of the invention are set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE FIGURES

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description serve to explain the principles of the invention.

FIGS. **1** and **2** depict a representative process for manufacturing the formulations of the present invention, as described in greater detail in Example 4.

DETAILED DESCRIPTION

Definitions and Use of Terms

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon.

As used in the specification and claims, the singular forms a, an, and the include plural references unless the context clearly dictates otherwise. For example, the term "a pharmaceutical excipient" refers to one or more pharmaceutical excipients for use in the presently disclosed formulations and methods.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

When used herein the term "about" will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength due to manufacturing variation and time-induced product degradation. In one embodiment the term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent to the recited strength. In another embodiment the term allows for any variation within 5% of the recited strength or concentration of the formulation.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder (collectively "disorder"). This term includes active treatment, that is, treatment directed specifically toward the improvement of a disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the disorder.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise unde-

sirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. "Pharmaceutically acceptable salts" means salts that are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity.

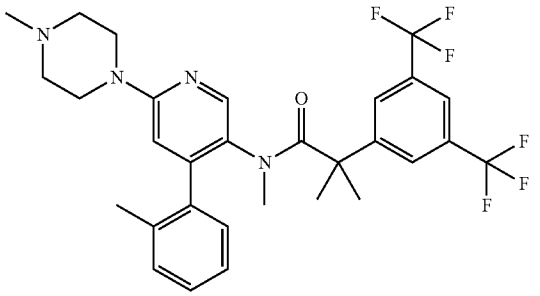
When a weight of an active ingredient is given without reference to the free base or salt of the active ingredient, it will be understood that the weight can refer to the weight of the free base or the weight or the entire salt. In like manner, when the molecule can exist as a hydrate, and the weight of the molecule is given, it will be understood that the weight can be refer to the weight of the hydrate or the weight of the molecule without the waters of hydration.

"Disodium edetate" refers to anhydrous disodium edetate or any of its hydrated forms.

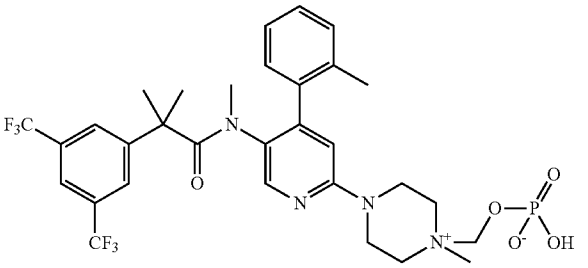
The term "liquid formulation" or "liquid solution" or "injectable solution," or words of similar import, when used in reference to a fosnetupitant injectable solution, refers to any liquid formulation of fosnetupitant that is suitable for intravenous injection. The solution can be manufactured as a liquid and packaged as such, or it can be a formulation that is intended for lyophilization, or a lyophilized formulation reconstituted in water.

Unless differently specified, the term "concentration" means herein the amount of a product present in a volume of solution; when concentration values are given for a lyophilized powder, the concentration values are intended to be based on reconstitution of the powder with a suitable reconstitution volume of water, i.e. the lyophilized powder contains the given product in amounts providing the given concentration values once the powder is dissolved in the reconstitution volume; suitable reconstitution volumes may typically range from 1 to 30 mL, preferably from 3 to 25 mL, more preferably from 8 to 22 mL, such as 19-21 mL or 9-11 mL, for example 10±1 mL or 20±1 mL; other typical reconstitution volumes are 10-30 mL, or 15-25 ml, or about 20 mL.

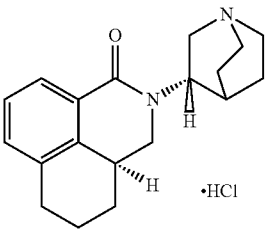
"Netupitant" refers to 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridine-3-yl)propanamide. The compound has a molecular weight of 579 g/mol, and the following chemical structure:



Fosnetupitant refers to 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl) piperazin-1-ium, also referred herein as p-Netu, 08-PNET or API. The compound has the following chemical structure:



"Palonosetron" refers to (3aS)-2-[(S)-1-azabicyclo [2.2.2] oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxolHbenz[de]isoquinoline. The hydrochloride salt has the following chemical structure:



Discussion of Principal Embodiments

The invention can be defined based on several principal embodiments which can be combined in any manner physically and mathematically possible to create additional principal embodiments.

In a first principal embodiment the invention provides a pharmaceutically stable injectable formulation of fosnetupitant and netupitant at a balanced ratio comprising: (a) from 95 to 99.99 weight parts fosnetupitant or a pharmaceutically acceptable salt thereof; and (b) from 0.01 to 5 weight parts netupitant or a pharmaceutically acceptable salt thereof; and (c) pH adjusting means for maintaining said physiologically balanced ratio; wherein, when the formulation is a liquid formulation, said fosnetupitant or pharmaceutically acceptable salt thereof is completely dissolved in said formulation.

In another principal embodiment, the invention provides a liquid injectable formulation of fosnetupitant comprising: (a) from 2.3 to 30 mg/mL of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base; (b) optionally, from 5 to 30 μg/mL of palonosetron or a pharmaceutically acceptable salt thereof, based on the weight of the free base; (c) sodium hydroxide; (d) disodium edetate; (e) optionally hydrochloric acid; (f) mannitol; and (g) water q.s.

Another principal embodiment provides a liquid injectable formulation of fosnetupitant comprising: (a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant, based on the weight of the free base; (b) optionally from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base; (c) from 0.05 to 0.9 mg/mL disodium edetate (based on the anhydrous form; (d) from 10 to 100 mg/mL mannitol; (e) NaOH and optionally HCl q.s. to pH 7.0-10.0; and (f) water q.s.

Another principal embodiment provides a lyophilized powder injectable formulation of fosnetupitant comprising, when reconstituted in water to a suitable volume: (a) from 2.3 to 30 mg/mL of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base;

(b) optionally, from 5 to 30 μg/mL of palonosetron or a pharmaceutically acceptable salt thereof, based on the weight of the free base; (c) sodium hydroxide; (d) disodium edetate; (e) optionally hydrochloric acid; (f) mannitol;

Still another principal embodiment provides a lyophilized powder injectable formulation of fosnetupitant comprising, when reconstituted in water to a suitable volume: (a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant, based on the weight of the free base; (b) optionally from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base; (c) from 0.1 to 2.0 mg/mL disodium edetate (based on the anhydrous form); (d) from 10 to 100 mg/mL mannitol; and (e) NaOH and optionally HCl q.s. to pH 7.0-10.0.

In another principal embodiment, the invention provides a sealed preservative-free vial for a single administration of fosnetupitant comprising: (a) from 100 to 600 mg of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base; and (b) optionally, from 100 to 300 μg of palonosetron or a pharmaceutically acceptable salt thereof, based on the weight of the free base. The formulation within the vial can be a liquid solution or lyophilized powder. A particularly preferred amount of fosnetupitant or a pharmaceutically acceptable salt thereof is 235 mg based on the weight of the free base. Conversely, the invention provides a method of treating emesis by administering an intravenous dose of approximately 235 mg of fosnetupitant, or a pharmaceutically acceptable salt thereof, based on the weight of the free base of fosnetupitant.

In another principal embodiment the invention provides a method of manufacturing an injectable formulation of fosnetupitant comprising: (a) admixing the chloride hydrochloride salt of fosnetupitant with sodium hydroxide in water at a basic pH to form a solution; (b) reducing the pH of the solution by the addition of one or more acidic pH adjusting agents, preferably to a pH still above 7; and (c) optionally admixing the solution with one or more pharmaceutically acceptable excipients, optionally followed by lyophilization.

Discussion of Formulation Subembodiments

The invention can further be understood with reference to various subembodiments which can modify any of the principal embodiments. These subembodiments can be combined in any manner that is both mathematically and physically possible to create additional subembodiments, which in turn can modify any of the principal embodiments. For example, any aspect of the formulation given below can be used to further define a liquid solution of the principal embodiments, or a lyophilized powder of the principal embodiments. To the extent the preferred liquid and lyophilized formulations differ, those differences will be called out specifically in the subembodiments.

In any of the foregoing embodiments, the fosnetupitant is preferably present as the chloride hydrochloride salt. However, it will be understood that the fosnetupitant can also be present in the formulation as the free base or any other pharmaceutically acceptable salt. It will also be understood that the salt can disassociate in a liquid medium into ion/counter-ion pairs, and still constitute a "salt" as that term is used in the present document according to industry custom.

Various subembodiments can also be defined based on the concentration of fosnetupitant in the solution. In one subembodiment, the concentration of fosnetupitant or pharmaceutically acceptable salt thereof in solution is from 4.5 to 27 mg/mL based on the weight of the free base. In other subembodiments, the concentration of fosnetupitant in the solution ranges from 6 to 26 mg/mL, 8 to 20 mg/mL, or 10 to 15 mg/mL, based on the weight of the free base. In a particularly preferred embodiment, when 20 ml of formulation is contained in a single use vial, the formulation comprises approximately 11.76 mg/mL fosnetupitant (based on the weight of the free base) or 13 mg/mL fosnetupitant (based on the weight of the chloride hydrochloride salt). When the formulation is a lyophilized powder the foregoing concentrations are preferably based on a 20 mL reconstitution volume in water.

Various subembodiments can also be defined based on the ratio of netupitant to fosnetupitant in the formulation. The netupitant and fosnetupitant are preferably present in a weight ratio greater than 0.01:99.99 (0.01 weight parts netupitant and 99.99 weight parts fosnetupitant). The weight ratio of netupitant to fosnetupitant is preferably less than 5:95, 4:96, 3:97, 2:98, 1:99, or 0.5:99.5.

Other subembodiments can be defined based on the pH of the formulation. All the present formulations typically have a pH ranging from 7 to 10. In a detailed embodiment, the pH interval ranges from >7.0 up to 10.0. One preferred pH interval is from 8.5 to 9.5. Further sub-ranges are also contemplated, i.e. from >7.0 to 7.5 or from 7.5 to 8.0, or from 8.0 to 8.5, or from 8.5 to 9.0, or from 9.0 to 9.5, or from 9.5 to 10, and combinations of these end-points.

Other subembodiments can be defined based on combinations of acidifying and alkalizing agents used as the "pH adjusting means." At least one alkalizing agent should be present among the pH adjusting means to assure a high enough pH to dissolve the fosnetupitant, but not so high that the fosnetupitant is hydrolyzed to netupitant outside the weight ratios described herein, or other unwanted degradation occurs.

A particularly preferred pH adjusting means is sodium hydroxide, although other alkalizing agents could be used including ammonia, calcium hydroxide, diethanolamine, monoethanolamine, potassium bicarbonate, potassium citrate, potassium hydroxide, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate dihydrate, dimeglumine, tris(hydroxymethyl)aminomethane, and triethanolamine. Any of these alkalizing agents should be used in a concentration adequate to impart a pH of approximately 11 to 14 (preferably 12) after the addition of fosnetupitant to its target concentration. In a 11.76 mg/mL fosnetupitant formulation (based on the weight of the free base), the sodium hydroxide concentration used for its dissolution will typically range from 1.5 to 3.0 mg/mL, from 2.0 to 2.5 mg/mL, or about 2.18 mg/mL.

The pH adjusting means may also comprise one or more acidifying agents to reduce the pH of the solution after the fosnetupitant is completely solubilized during the manufacturing process, and stabilize the formulation during storage. Exemplary acidifying agents include adipic acid, ammonium chloride, citric acid monohydrate, glacial acetic acid, hydrochloric acid, lactic acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid, as well as edetic acid and its various salts.

In one embodiment the pH adjusting means includes hydrochloric acid, and it is present if necessary in an amount sufficient to adjust the pH within the range 7 to 10 after the fosnetupitant and sodium hydroxide are combined. Thus, the final amount of added hydrochloric acid will typically equal from 0.5 to 3.0 liters or from 1.0 to 2.0 liters or about 1.5 liters (on a 1.0 M basis) per 300 liters of solution.

In one embodiment the pH adjusting means includes only an alkalizing agent. In another embodiment the pH adjusting means includes an alkalizing agent and an acidifying agent.

In another embodiment, the pH adjusting means includes an alkalizing agent and two acidifying agents.

The above referred amounts of pH adjusting means are herein intended as the amounts used during the manufacturing of the formulation to adjust the pH to the requested pH values; these amounts do not necessarily correspond to those present in the final composition because the pH adjustment involves a consumption of the acidic/basic reagents used for this purpose.

Other subembodiments can be based on the concentration of disodium edetate in the formulation. This component was found surprisingly effective in preventing the hydrolytic conversion of p-Netu to netupitant, as well as unwanted formation of opalescence in the solution after its manufacturing and/or during storage; this advantageously allowed to formulate fosnentupitant at final pH values relatively close to neutrality (a feature particularly appreciated for formulations administrable to patients) without risk of precipitation of fosnentupitant and/or related by-products.

When present in a liquid formulation, the concentration of disodium edetate preferably ranges from 0.05 to 0.9 mg/mL, from 0.1 to 0.25 mg/mL, or from 0.125 to 0.2 mg/mL, based on the anhydrous form. Alternatively, the concentration of disodium edetate preferably ranges from 0.1 to 2.0 mg/mL, from 0.2 to 0.5 mg/mL, or from 0.25 to 0.4 mg/mL. In a first preferred variant, the concentration of disodium edetate is 0.16 mg/mL based on the anhydrous form (or 0.18 mg/mL based on the dihydrate form); another preferred concentration of disodium edetate is 0.32 mg/mL based on the anhydrous form (or 0.35 mg/mL based on the dihydrate form). In a second preferred variant, the preferred concentration of disodium edetate is 0.14 mg/mL based on the anhydrous form (or 0.16 mg/mL based on the dihydrate form); another preferred concentration of disodium edetate is 0.29 mg/mL based on the anhydrous form (or 0.32 mg/mL based on the dihydrate form).

When present in a lyophilized formulation, the concentration of disodium edetate preferably ranges from 0.05 to 0.9 mg/mL, from 0.1 to 0.25 mg/mL, or from 0.125 to 0.2 mg/mL, based on the anhydrous form. Alternatively, the concentration of disodium edetate preferably ranges from 0.1 to 2.0 mg/mL, from 0.2 to 0.5 mg/mL, or from 0.25 to 0.4 mg/mL. In a first preferred variant, the concentration of disodium edetate is 0.16 mg/mL based on the anhydrous form (or 0.18 mg/mL based on the dihydrate form); another preferred concentration of disodium edetate is 0.32 mg/mL based on the anhydrous form (or 0.35 mg/mL based on the dihydrate form). In a second preferred variant, the preferred concentration of disodium edetate is 0.14 mg/mL based on the anhydrous form (or 0.16 mg/mL based on the dihydrate form); another preferred concentration of disodium edetate is 0.29 mg/mL based on the anhydrous form (or 0.32 mg/mL based on the dihydrate form). The foregoing concentrations are based on a suitable reconstitution volume in water, typically 10-30 mL, or 15-25 ml, and most preferably about 20 mL.

The formulation can also include palonosetron or a pharmaceutically acceptable salt thereof, and in a preferred embodiment includes palonosetron hydrochloride. The concentration of palonosetron preferably ranges from 1 to 100 μg/mL, from 2 to 50 μg/mL, from 5 to 50 μg/mL, from 5 to 30 μg/mL, or from 10 to 20 μg/mL, based on the weight of the free base. The palonosetron is most preferably present as palonosetron hydrochloride, and is most preferably present at a concentration of approximately 14.04 μg/mL based on the weight of the hydrochloride salt. When the formulation is a lyophilized powder the foregoing concentrations are based on a suitable reconstitution volume in water, as previously described, typically 10-30 mL, or 15-25 ml, or about 20 mL.

In another embodiment the concentration of palonosetron is proportional to the concentration of netupitant. Thus, in a particularly preferred embodiment the formulation includes 0.28 μg of palonosetron hydrochloride for every 260 mg of the chloride hydrochloride salt of fosnetupitant. In other embodiments, the formulation includes from 0.10 to 1.0 μg or from 0.25 to 0.75 μg of palonosetron hydrochloride (based on the weight of the free base) for every 200 to 450 mg of the chloride hydrochloride salt of fosnetupitant.

Still further subembodiments can be defined based on the bulking agent that can be present in the formulation, and which is always present when the formulation is lyophilized. In various embodiments, the bulking agent comprises mannitol, polyvinylpyrrolidone (PVP), lactose, cellulose, or glycine. A preferred bulking agent is mannitol, and it is preferably present in a concentration of from 10 to 100 mg/mL, from 20 to 70 mg/mL, or from 30 to 50 mg/mL, most preferably 38 mg/mL. When the formulation is a lyophilized powder, this concentration is based on a suitable volume of reconstitution in water, as previously described, typically 10-30 mL, or 15-25 ml, or about 20 mL. The bulking agent also preferably functions as a tonicity agent, and is preferably present in an amount sufficient to render the formulation isotonic.

The formulation is preferably an aqueous-based formulation, with the ingredients combined and dissolved in water for injection. The formulation can also be present as a lyophilized powder. Either formulation is preferably isotonic. The lyophilized formulation preferably has the same active and inactive excipients as the aqueous formulation, in the same relative concentrations, except that the water has been freeze-dried from the formulation; in a variant, the amount of disodium edetate present in lyophilized formulations is higher (typically double) than the amount used in the aqueous formulations.

The formulation is preferably present in a single use container such as a vial, particularly a preservative-free vial, although preservatives could be present, particularly when packaged in a multi-use vial. The formulation and its container are also preferably sterile, during and after packaging. The formulation and container can be aseptically sterilized or terminally sterilized.

When present in a fixed dose container, the formulation can also be characterized by the quantity of fosnetupitant present. Thus, in various subembodiments a single use fixed dose container will contain from about 100 to about 500 mg of fosnetupitant or a pharmaceutically acceptable salt thereof, from about 150 to about 350 mg, or from about 200 to about 300 mg. Most preferably the single use container will contain approximately 235 mg of fosnetupitant or a pharmaceutically acceptable salt thereof, based on the weight of the free base, or approximately 260 mg of the chloride hydrochloride salt of fosnetupitant.

Methods of Treatment

Other subembodiments relate to the use of any of the foregoing formulations for the treatment of diseases modulated by the NK-1 receptor. A particularly preferred use is to treat nausea or emesis, particularly associated with chemotherapy (i.e. chemotherapy induced nausea and vomiting). The New England Journal of Medicine, Vol. 340, No. 3 190-195 (1999) has described the reduction of cisplatin-induced emesis by a selective NK-1 receptor antagonist.

Other uses also are possible. For example, the central and peripheral actions of the mammalian tachykinin substance P,

the naturally occurring ligand for the NK-1 receptor, have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645). Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases has also emerged ("Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13,23-93, 1993). Other examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis. See WO 95/16679, WO 95/18124 and WO 95/23798.

Therefore, in various subembodiments, the invention provides a method of modulating substance-P activity, or treating a disease mediated by substance-P activity, by administering a therapeutically effective dose of any of the foregoing formulations or dosing units. A therapeutically effective dose preferably comprises from 100 to 500 mg of fosnetupitant or a pharmaceutically acceptable salt thereof, and preferably comprises from 200 to 300 mg of fosnetupitant or pharmaceutically acceptable salt thereof. In a particularly preferred embodiment, the therapeutically effective dose comprises 260 mg of the chloride hydrochloride salt of fosnetupitant, administered intravenously, based on the weight of the salt. Preferred diseases treatable by these methods include nausea, emesis and chemotherapy induced nausea and vomiting.

Prior to administration, the formulation is preferably reconstituted with an infusion solution to provide a 30 minute infusion. Suitable infusion solutions include, for example, 5% glucose and 0.9% NaCl. When reconstituted in either of the infusions, the final concentration of fosnetupitant or pharmaceutically acceptable salt thereof will preferably range from 0.5 to 13.0 mg/mL, or from 2.0 to 8.0 mg/mL. In a particular preferred embodiment the concentration in the infusion solution will preferably be approximately 5.2 mg/mL, based on the weight of the chloride hydrochloride salt of fosnetupitant.

EXAMPLES

In the following examples, efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. P-Netu (or API or 08-PNET) refer to the chloride hydrochloride salt of fosnetupitant. Disodium edetate ("EDTA") quantities are reported based on the weight of the dihydrate. 14-netu refers to netupitant. Palo refers to palonosetron HCl with concentrations reported based on the free base

Example 1. Effect of Netupitant Concentrations

A study was undertaken to determine the maximum allowable concentration of netupitant in aqueous solutions of p-Netu, above which unacceptable precipitation is observed. Based on p-Netu solubility studies indicating that p-Netu solubility drops significantly in water at acidic pH values less than 7.0, and chemical teachings that high pH values will contribute to the hydrolysis of p-Netu to its parent molecule, a solution pH of 7.8 was selected for this example. p-Netu was formulated at a concentration of 13 mg/mL and a pH of 7.8 The results are reported in Table 1.

TABLE 1

Spiking of Netupitant into p-Netu Solution	Appearance
0%	Clear solution
0.5% (0.065 mg/mL)	Clear solution
1% (0.13 mg/mL)	Clear solution
1.5% (0.195 mg/mL)	Slightly opalescent solution
2% (0.26 mg/mL)	Slightly opalescent solution
3% (0.39 mg/mL)	Suspension
4% (0.52 mg/mL)	Suspension
5% (0.65 mg/mL)	Suspension

Based on these studies, a netupitant concentration of 2.5-3% was determined as the limit for appreciable precipitation in a 13 mg/mL p-Netu solution (maximum ratio ca. 1:50 netu:p-Netu).

Example 2. Formulation Development Studies

Numerous development formulations were prepared and tested, both as liquid solutions and after lyophilization. These studies established the following preliminary trends:

- Increasing the API concentration leads to a more degraded lyophilised product.
- The mother solutions are more stable than the corresponding freeze dried product; this is surprising for a product susceptible to hydrolytic degradation.
- The presence of buffers, especially phosphates, causes greater hydrolysis.
- An initial lower concentration of netupitant does not prevent degradation.

Example 3. Factoral Formulation Study

Based on the preliminary results of Example 2, a factoral formulation study was undertaken to investigate the impact of API concentration, disodium edetate and PVP and Tween 80 as surfactants, at pH 8.5-9.5. The formulations are described in Tables 2a and 2b.

TABLE 2a

Ingredients	Formulations F1* Amount	F2 Amount	F3 Amount	F4 Amount	F5 Amount	F6 Amount	F7 Amount	F8 Amount	F9 Amount
API									
08-PNET (mg/mL)	5	26	15.5	5	26	26	26	5	5
Excipients									
PVP K12 (% v/v)	0	0	1	0	2	2	0	2	2
EDTA disodium salt (% w/v)	0.127	0.127	0.064	0	0	0.127	0	0	0.127
Tween 80 (% w/v)	0	0.5	0.25	0.5	0.5	0	0	0	0.5

TABLE 2b

Ingredients	Formulations F10 Amount	F11 Amount	F12 Amount	F13 Amount	F14 Amount	F15 Amount	F16 Amount	F17 Amount	F18 Amount	F19 Amount
API										
08-PNET (mg/mL)	5	26	26	26	5	15.5	5	5	26	15.5
Excipients										
PVP K12 (% v/v)	0	2	2	NA	2	1	0	2	0	0
EDTA disodium salt (% w/v)	0	0	0.127	0.127	0.127	0.064	0.127	0	0	0
Tween 80 (% w/v)	0	0	0.50	0	0	0.25	0.50	0.50	0.50	0

The solutions were evaluated for a month at 40° C. and 75% RH and at 25° C. and 60% relative humidity. After 30 days all the solutions at 40° C. were clear and about half of those at room temperature were limpid. The results are presented in Table 2c.

TABLE 2c

	Storage Conditions (30 days)	%14-Netu amount
F1	40° C./75% RH	1.2
	25° C./60% RH	1.2
F1b	40° C./75% RH	1.5
	25° C./60% RH	1.3
F2	40° C./75% RH	1.3
	25° C./60% RH	opalescent
F3	40° C./75% RH	1.4
	25° C./60% RH	1.2
F4	40° C./75% RH	1.2
	25° C./60% RH	0.9
F5	40° C./75% RH	1.5
	25° C./60% RH	opalescent
F6	40° C./75% RH	1.4
	25° C./60% RH	opalescent
F7	40° C./75% RH	1.5
	25° C./60% RH	opalescent
F8	40° C./75% RH	1.8
	25° C./60% RH	opalescent
F9	40° C./75% RH	1.0
	25° C./60% RH	0.9
F10	40° C./75% RH	1.7
	25° C./60% RH	1.8
F11	40° C./75% RH	1.5
	25° C./60% RH	opalescent
F12	40° C./75% RH	1.4
	25° C./60% RH	opalescent
F13	40° C./75% RH	1.5
	25° C./60% RH	opalescent
F14	40° C./75% RH	1.4
	25° C./60% RH	opalescent
F15	40° C./75% RH	1.4
	25° C./60% RH	1.2
F16	40° C./75% RH	1.2
	25° C./60% RH	0.9
F17	40° C./75% RH	2.9
	25° C./60% RH	1.0
F18	40° C./75% RH	1.6
	25° C./60% RH	opalescent
F19	40° C./75% RH	1.5
	25° C./60% RH	1.3

Further experiments have shown that the presence of EDTA reduced, in proportion to its concentration in solution, the conversion of p-Netu to 14-Netu, with a corresponding stabilization of the solution which remained clear throughout the whole testing period.

Example 4. Exemplary Formulations

Exemplary lyophilized and liquid formulations based on the studies described in the previous examples are presented below in Tables 3a to 3c; in these tables the quantities of EDTA are based on its dihydrated disodium salt.

TABLE 3a

(lyophilized formulation)

Ingredient	Concentration	Purpose
p-Netu	13 mg/mL	Active
Palo HCl (optional)	14.04 µg/mL	Active
EDTA	0.32 mg/mL	Chelating agent
Mannitol	38 mg/mL	Bulking agent

TABLE 3a-continued

(lyophilized formulation)

Ingredient	Concentration	Purpose
NaOH (0.5M)	q.s. for p-Netu dissolution and pH adjustment	p-Netu dissolution and pH adjustment
HCl (0.1M and 1.0M)	q.s. for pH adjustment	pH adjustment
WFI	q.s. to 1 mL	Solvent (removed during lyophilization)

The lyophilized product unit contains 20 times the above amounts, to be reconstituted with 20 mL of water
* 13 mg of p-Netu corresponding to 11.8 mg fosnetupitant free base (Ratio 1.106:1)
** 14.04 μg of palonosetron HCl corresponding to 12.5 μg of palonosetron free base (Ratio 1.123:1)

TABLE 3b

(liquid injectable formulation)

Ingredient	Concentration	Amount per vial ***
p-Netu	26 mg/mL	273 mg *
Palo HCl (optional)	28.08 μg/mL	294.84 μg **
EDTA	0.32 mg/mL	3.36 mg
Mannitol	25 mg/mL	262.5 mg
NaOH (0.5M)	q.s. for p-Netu dissolution	
HCl (0.1M and 1.0M)	q.s. for pH adjustment	
WFI	q.s. to 1 mL	10.5 mL

10.5 mL of the solution are used for filling the Vial
* 273 mg of p-Netu corresponding to 246.8 mg fosnetupitant free base (Ratio 1.106:1)
** 294.84 μg of palonosetron HCl corresponding to 262.5 μg of palonosetron free base (Ratio 1.123:1)
*** Labeled amounts: 260.0 mg of fosnetupitant and 0.250 mg of palonosetron free base

TABLE 3c

(liquid injectable formulation)

Ingredient	Concentration	Amount per vial ***
p-Netu	13 mg/mL	267.8 mg *
Palo HCl (optional)	14.04 μg/mL	289.22 μg **
EDTA	0.16 mg/mL	3.30 mg
Mannitol	38 mg/mL	782.8 mg
NaOH (0.5M)	q.s. for p-Netu dissolution	
HCl (0.1M and 1.0M)	q.s. for pH adjustment	
WFI	q.s. to 1 mL	20.6 mL

20.6 mL of the solution are used for filling the Vial
* 267.8 mg of p-Netu corresponding to 242.1 mg fosnetupitant free base (Ratio 1.106:1)
** 289.22 μg of palonosetron HCl corresponding to 257.5 μg of palonosetron free base (Ratio 1.123:1)
*** Labeled amounts: 260.0 mg of fosnetupitant and 0.250 mg of palonosetron free base

Three further formulations were prepared (the first being a lyophilized formulation while the second and third being liquid injectable formulations) whose compositions were identical to those respectively reported in Tables 3a, 3b and 3c, with the sole difference that the weight of EDTA disodium salt (i.e. 0.32, 0.32 and 0.16 mg/mL respectively) was that of the anhydrous product (i.e. the EDTA disodium salt in its non-hydrated form): each of these formulations represents a further embodiment of the present invention.

Example 5. Manufacturing Protocol

The protocol for manufacturing the formulation described in Example 4 is described below and depicted in FIGS. **1** and **2**. Two 325 liter tanks are used to carry out solution preparation. The mixing system of the compounding vessel consists of a magnetic stirring system. This system is equipped with a propeller-shaped mixing head placed at the bottom of the tank and moved by a magnetic rotating field. The preparation steps are as follows:

1. The compounding vessel is loaded with WFI (at 20±5° C.) up to a mass of 40±1 kg.
2. 654 g of solid NaOH is added to the compounding vessel.
3. After the dissolution of the NaOH, the compounding vessel is loaded with WFI (at 20±5° C.) up to a mass of 183 kg±1 kg (ca. 60% of the final volume).
4. The solution is mixed for 10 minutes. The pH of the solution in the compounding vessel is raised to the target pH of ca.13 (pH range: 11-14).
5. p-Netu is slowly added inside the compounding tank.
6. pH is checked at room temperature (22±5° C.). Because the addition of p-Netu tends to lower the pH, manual titration can be performed using an amount of NaOH 0.5M to reach a pH value within the range 9-13, with 12 as the target pH.
7. After the dissolution of the p-Netu, pH is checked at room temperature (22±1° C.) and adjusted if necessary to the range 9-13, with 12 as target point.
8. 96 g of EDTA disodium salt dihydrate is added to the compounding tank and the solution stirred until complete dissolution.
9. After EDTA addition, pH is checked at room temperature (24±1° C.) and adjusted if necessary to 9.00±0.50 with HCl (0.1 and 1.0M) or NaOH 0.5M.
10. 11.4 kg of mannitol is added to the compounding tank.
11. The palonosetron HCl weighed in the dispensing area is solubilized in a glass beaker using 490 g of WFI, in p-Netu-Palo Combo solution preparation room.
12. Palonosetron HCl solution is added inside the compounding tank.
13. After palonosetron HCl addition, pH is checked again at room temperature (24° C.±1) and adjusted if necessary to 9.00±0.50 with HCl (0.1 and 1.0M) or NaOH 0.5M.
14. Eventually, the final QS weight is achieved by loading WFI into the tank at RT.
15. The p-Netu-Palo combination solution is brought to the final volume (300 L→305.7 kg) by means of WFI.

Lyophilization is undertaken using a standard lyophilization cycle. Briefly, the lyophilization cycle takes place in a 33 m^2 BOC Edwards freeze-dryer using bottomless trays. The partially stoppered vials are loaded into the BOC Edwards 33" freeze dryer at 5±3° C. Each tray is loaded with 47 vials and each shelf with 30 bottomless trays. When drying is completed, sterile filtered nitrogen is injected into the chamber through a sterile 0.22 micron filter. The vials are automatically stoppered in the chamber, unloaded, and then transported by means of a laminar flow trolley to the capping machine where the vials are loaded on a turntable (which feed the capping machine).

Example 6. Stability Testing

The lyophilized and liquid formulations as described in Example 4 were tested for stability and the results reported below in Tables 4a, 4b and 4c.

TABLE 4a

(lyophilized formulation of Example 4, table 3a)

Test	T = 0	1M-	3M 5° C.;	6M 5° C.;	12M 5° C.;	18M 5° C.	24M 5° C.
		25° C./60% RH;	25° C./60% RH;	25° C./60% RH;	25° C./60% RH	—	—
		30° C./65% RH;	30° C./65% RH	30° C./65% RH	—	—	—
		40° C./75% RH	—	—	—	—	—
pH	9.6	—	9.7	9.6	9.7	9.7	9.7
		9.8	9.6	9.7	9.5	—	—
		9.8	9.6	9.5	—	—	—
		9.6	—	—	—	—	—
Appearance	Clear	—	clear	clear	clear	clear	clear
reconstituted		clear	clear	clear	clear	—	—
solution		clear	clear	clear	—	—	—
		clear	—	—	—	—	—
Osmolarity	336	—	317	308	308	316	303
		302	312	330	320	—	—
		302	309	312	—	—	—
		296	—	—	—	—	—
KF (%)	0.29	—	0.36	0.34	0.31	0.29	0.35
		0.48	0.40	0.44	0.65	—	—
		0.44	0.46	0.52	—	—	—
		0.40	—	—	—	—	—
%14-Netu	0.82	—	0.76	0.87	0.85	0.87	0.97
		1.07	1.33	1.76	2.59	—	—
		1.30	1.97	2.81	—	—	—
		2.50	—	—	—	—	—
Assay 08-	270.4	—	259.9	262.7	270.0	261.2	255.6
PNET		262.6	258.3	260.8	269.5	—	—
(mg/vial)		259.4	260.8	253.6	—	—	—
		257.3	—	—	—	—	—
Assay Palo	0.245	—	0.255	0.254	0.271	0.252	0.239
(mg/vial)		0.247	0.250	0.252	0.248	—	—
		0.245	0.249	0.250	—	—	—
		0.237		—	—	—	—
Related	—	—	—	<LOQ	<LOQ	<LOQ	<LOQ
Substances %		—	—	<LOQ	<LOQ	—	—
(Palo)		—	—	<LOQ	—	—	—
		—	—	—	—	—	—

TABLE 4b

(lyophilized formulation of Example 4, table 3b)

Test	T = 0	1M-	3M 5° C.;	6M 5° C.;	9M 5° C.;	12M 5° C.
		25° C./60% RH;	25° C./60% RH;	25° C./60% RH;	25° C./60% RH	—
		30° C./65% RH;	30° C./65% RH	30° C./65% RH	—	—
		40° C./75% RH	—	—	—	—
pH	9.4	9.2	9.3	9.3	9.2	9.3
		9.2	9.3	9.2	—	—
		9.2	9.2	9.0	—	—
Appearance	clear	clear	clear	clear	clear	clear
reconstituted		clear	clear	clear	—	—
		clear	clear	clear	—	—
Osmolarity	303	309	313	312	313	312
(mOsm/kg)		313	310	312	—	—
		308	313	313	—	—
%14-Netu	0.46	0.57	0.58	0.60	0.54	0.63
		0.58	0.61	0.66	—	—
		0.73	0.93	1.21	—	—
Assay 08-	26.3	25.6	26.6	26.1	26.4	25.2
PNET		26.1	26.7	26.1	—	—
(mg/ml)		28.3	26.6	25.8	—	—
Assay Palo	0.025	0.024	0.025	0.025	0.024	0.024
(mg/ml)		0.024	0.025	0.025	—	—
		0.024	0.024	0.024	—	—
Related	Not	<LOQ	<LOQ	<LOQ	RRT 0.28:0.42	RRT 0.28:0.47
Substances %	detectable					RRT 0.32:0.42
(Palo)		<LOQ	RRT 0.32:0.61	<LOQ	—	—
		<LOQ	08-PALOd1:0.40	08-PALOd1:0.62	—	—
			RRT 0.32:0.44			

TABLE 4c

(lyophilized formulation of Example 4, table 3c)

Test	T = 0	1M 25° C./60% RH; 1M 30° C./65% RH; 1M 40° C./75% RH	3M 25° C./60% RH; 3M 30° C./65% RH 3M 40° C./75% RH	6M 25° C./60% RH; 6M 30° C./65% RH; 6M 40° C./75% RH	9M 25° C./60% RH	12M 25° C./60% RH	18M 25° C./60% RH
pH	9.4	9.1	9.1	9.1	9.0	9.1	—
		9.1	9.1	9.1	—	—	—
		9.0	8.9	8.8	—	—	—
Appearance of solution (5° C. clear without visible particles)	clear	clear	clear	clear	clear	clear	—
		clear	clear	clear	—	—	—
		clear	clear	clear	—	—	—
Osmolarity (mOsm/kg)	296	320	306	307	317	308	—
		302	306	307	—	—	—
		304	307	307	—	—	—
%14-Netu	0.46	0.55	0.59	0.59	0.65	0.65	—
		0.56	0.62	0.66	—	—	—
		0.67	0.96	1.32	—	—	—
Assay 08-PNET (mg/ml)	13.0	13.1	13.3	13.1	13.2	12.7	—
		13.2	13.3	13.0	—	—	—
		13.2	13.2	13.2	—	—	—
Assay Palo (mg/ml)		0.0127	0.0128	0.0125	0.0123	0.0124	—
		0.0125	0.0127	0.0125		—	—
		0.0124	0.0126	0.0123		—	—
Related Substances % (Palo)	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	0.40	—
		<LOQ	<LOQ	<LOQ	—	—	—
		<LOQ	<LOQ	<LOQ	—	—	—

OTHER EMBODIMENTS

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

The invention claimed is:

1. A pharmaceutically stable injectable liquid formulation of fosnetupitant comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) sodium hydroxide;

d) disodium edetate;

e) optionally hydrochloric acid; and

f) mannitol.

2. A pharmaceutically stable injectable lyophilized formulation of fosnetupitant comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) sodium hydroxide;

d) disodium edetate;

e) optionally hydrochloric acid; and

f) mannitol.

3. A pharmaceutically stable liquid injectable solution formulation of fosnetupitant at a pH of 7.0-10.0 comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) from 0.05 to 0.9 mg/mL disodium edetate;

d) from 10 to 100 mg/mL mannitol;

e) NaOH;

optionally HCl; and

g) water q.s.

4. A pharmaceutically stable lyophilized powder injectable formulation of fosnetupitant at a pH of 7.0-10.0 comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) from 0.1 to 2.0 mg/mL disodium edetate;

d) from 10 to 100 mg/mL mannitol; and

e) NaOH and optionally HCl;

based on a reconstitution in a suitable water volume.

5. The lyophilized powder formulation of claim **4** at a pH of 7.0-10.0, comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) from 0.1 to 2.0 mg/mL disodium edetate;

d) from 10 to 100 mg/mL mannitol; and

e) NaOH and HCl;

based on a reconstitution in a suitable water volume.

6. The lyophilized powder formulation of claim **4** at a pH of 8.5-9.5, comprising:

a) about 13.0 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) about 14.04 μg/mL palonosetron hydrochloride based on the weight of the salt;

c) about 0.32 mg/mL disodium edetate;

d) about 38 mg/mL mannitol; and

e) NaOH and optionally HCl;

based on a reconstitution in water volume of 20 mL.

7. A method of manufacturing a liquid injectable or lyophilized formulation of fosnetupitant comprising:

a) simultaneously admixing the chloride hydrochloride salt of fosnetupitant with sodium hydroxide in water at a basic pH of from approximately 11 to 14 to form a solution;

b) reducing the pH of the solution to a basic pH of from approximately 7 to 10 by the addition of one or more acidic pH adjusting agents; and

c) optionally admixing the solution with one or more pharmaceutically acceptable excipients.

8. An intravenous formulation of fosnetupitant made by a process of mixing the fosnetupitant formulation of claim **2** with 0.9% saline or 5% glucose.

9. The liquid formulation of claim **1** comprising palonosetron hydrochloride and HCl.

10. The liquid formulation of claim **3**, comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) from 0.1 to 2.0 mg/mL disodium edetate;

d) from 10 to 100 mg/mL mannitol; and

e) NaOH and HCl.

11. The liquid formulation of claim **3** at a pH of 8.5-9.5, comprising:

a) about 13.0 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) about 14.04 μg/mL palonosetron hydrochloride based on the weight of the salt;

c) about 0.32 mg/mL disodium edetate;

d) about 38 mg/mL mannitol; and

e) NaOH and HCl.

12. The lyophilized powder formulation of claim **2** comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) from 0.1 to 2.0 mg/mL disodium edetate;

d) from 10 to 100 mg/mL mannitol; and

e) NaOH and optionally HCl;

based on a reconstitution in a suitable water volume.

13. The lyophilized powder formulation of claim **2** comprising:

a) about 13.0 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) about 14.04 μg/mL palonosetron hydrochloride based on the weight of the salt;

c) about 0.32 mg/mL disodium edetate;

d) about 38 mg/mL mannitol; and

e) NaOH and HCl;

based on a reconstitution in a suitable volume of water.

14. The liquid formulation of claim **1** at a pH of from 7.5 to 10.0.

15. The lyophilized powder formulation of claim **2** having a pH of from 7.5 to 10.0 upon reconstitution in water.

16. The lyophilized powder formulation of claim **12** having a pH of from 7.5 to 10.0 upon reconstitution in water.

17. The lyophilized powder formulation of claim **13** having a pH of from 7.5 to 10.0 upon reconstitution in water.

18. The method of claim **7**, wherein the acidic pH adjusting agent comprises hydrochloric acid.

19. A pharmaceutically stable injectable liquid formulation of fosnetupitant comprising:

a) from 2.3 to 30 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) from 5 to 50 μg/mL palonosetron hydrochloride based on the weight of the free base;

c) an alkalizing agent; and

d) an alkaline pH.

20. The pharmaceutically stable injectable liquid formulation of claim **19** comprising:

a) about 13.0 mg/mL of the chloride hydrochloride salt of fosnetupitant;

b) about 14.04 μg/mL palonosetron hydrochloride based on the weight of the salt;

c) sodium hydroxide as the alkalizing agent; and

d) a pH of from 7 to 10.

21. The pharmaceutically stable injectable liquid formulation of claim **19** comprising sodium hydroxide as the alkalizing agent and a pH of from 7 to 10.

* * * * *

Exhibit H

US010717721B2

(12) **United States Patent**
Fadini et al.

(10) **Patent No.: US 10,717,721 B2**
(45) **Date of Patent: *Jul. 21, 2020**

(54) **SUBSTITUTED PIPERAZINIUMS FOR THE TREATMENT OF EMESIS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 15/874,325, filed on Jan. 18, 2018, now Pat. No. 10,208,073, which is a continuation of application No. 15/194,984, filed on Jun. 28, 2016, now Pat. No. 9,908,907, which is a continuation of application No. 14/360,991, filed as application No. PCT/US2012/066778 on Nov. 28, 2012, now Pat. No. 9,403,772, which is a continuation-in-part of application No. 13/478,361, filed on May 23, 2012, now Pat. No. 8,426,450.

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**

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C07D 401/04	(2006.01)
A61K 31/496	(2006.01)
A61K 31/56	(2006.01)
A61K 45/06	(2006.01)
C07D 213/89	(2006.01)
A61K 31/44	(2006.01)
A61K 31/473	(2006.01)
A61K 31/675	(2006.01)
C07F 9/6509	(2006.01)
A61P 25/22	(2006.01)
A61P 13/10	(2006.01)
A61P 25/24	(2006.01)
A61P 1/08	(2006.01)
A61K 9/00	(2006.01)
A61K 31/573	(2006.01)

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(58) **Field of Classification Search**

CPC C07D 213/74; C07D 401/04

USPC 544/360; 546/308

See application file for complete search history.

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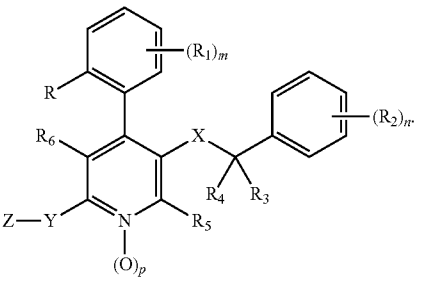
(57) **ABSTRACT**

Disclosed are compounds, compositions and methods for the prevention and/or treatment of diseases which are pathophysiologically mediated by the neurokinin (NK_1) receptor. The compounds have the general formula (I):

Formula (I)



2 Claims, 1 Drawing Sheet

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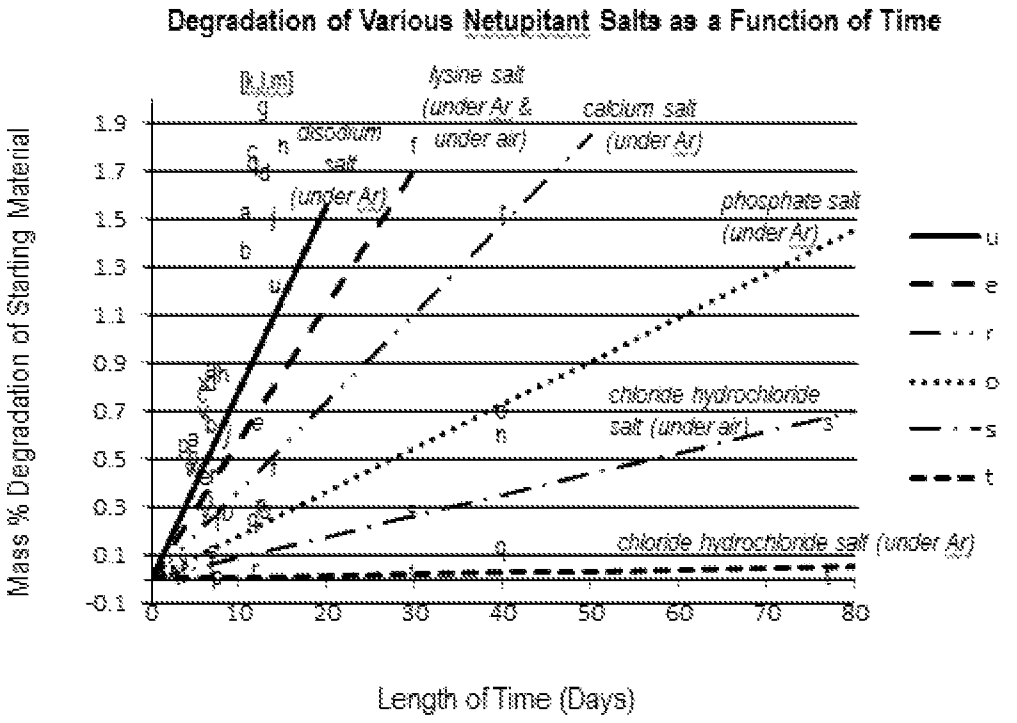


FIGURE 1: Degradation Behavior Over Time for Various Salts of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phos-phonooxy)methyl)piperazin-1-ium.

SUBSTITUTED PIPERAZINIUMS FOR THE TREATMENT OF EMESIS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

Description of Related Art

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et al. (*Science* 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis. Gesztesi et al. (*Anesthesiology* 93(4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis

U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron (a 5-HT_3 receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-oxide derivatives are reported in the '026 patent.

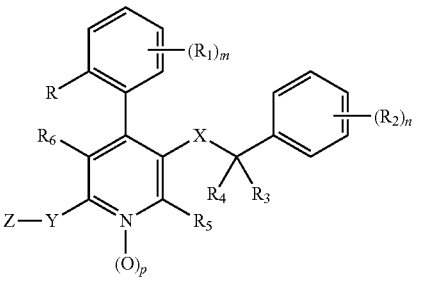
U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclose how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as prodrug structure(s), prodrug stability, synthetic cost, and selectivity of the phosphoryloxymethylation protocol.

In view of the above, there is a need to find new derivatives of and methods for making 4-phenyl-pyridine compounds that are effective NK_1 receptor antagonists, and that have enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives that are particularly well-suited for antagonizing the NK_1 receptor and that have the following general formula (I):

Formula (I)



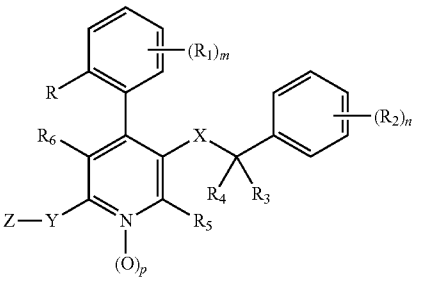
and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK_1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK_1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

In one embodiment the invention is a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof,

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocy-

cloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

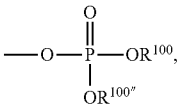
Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:

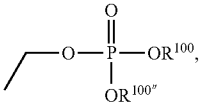
(Ia) —O^-,

(Ib) —OR^{100},

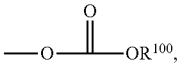
(Ic)



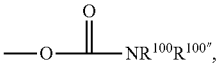
(Id)



(Ie)

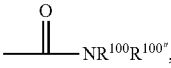


(If)

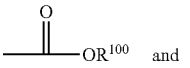


-continued

(Ig)

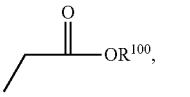


(Ih)



and

(Ii)



where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

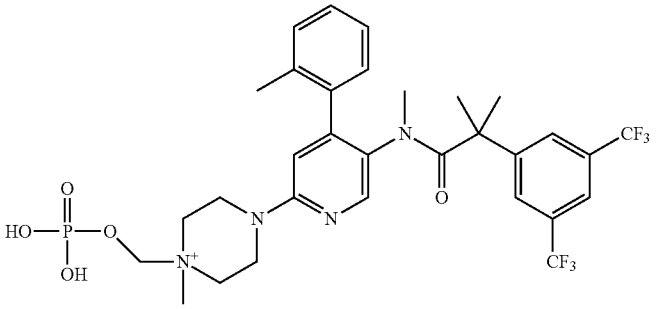
with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one.

In another embodiment the invention is the use of a therapeutically effective amount of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or adduct thereof, in the manufacture of a medicament which is able to treat emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof.

In an alternative embodiment the invention is a method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) as defined above.

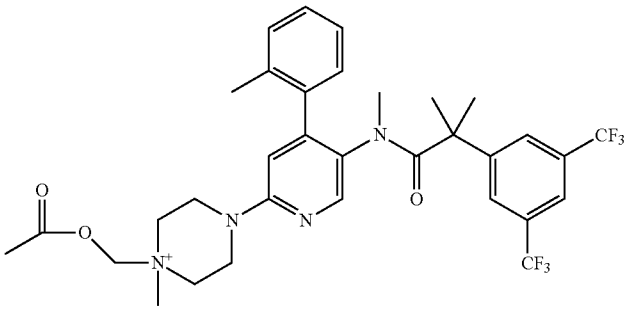
In still another embodiment the invention is a compound selected from the group consisting of:

GA1



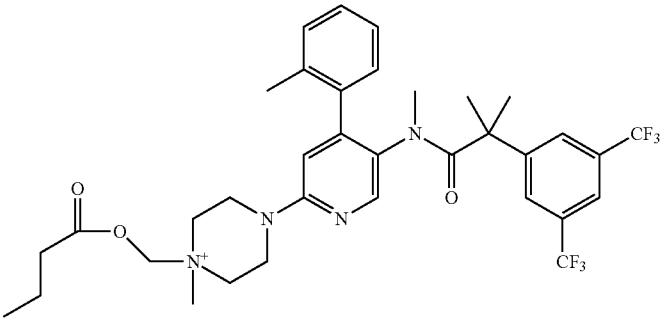
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,

GA2



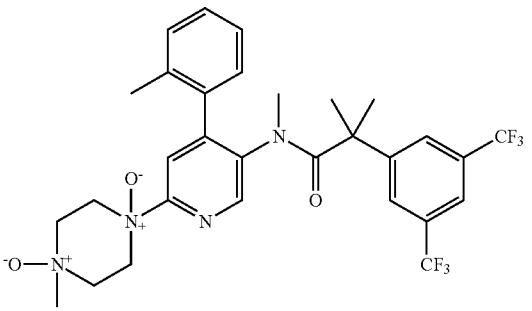
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,

GA3



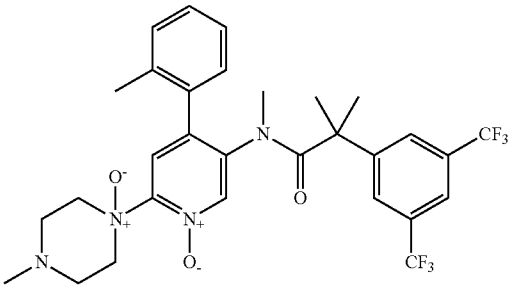
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,

GA4



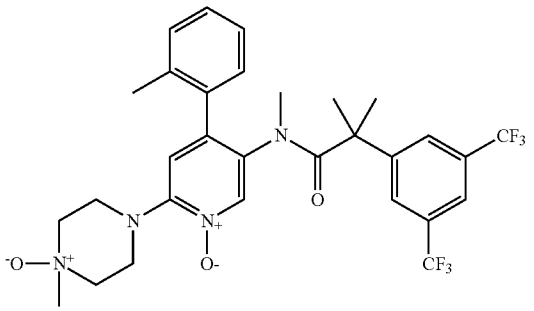
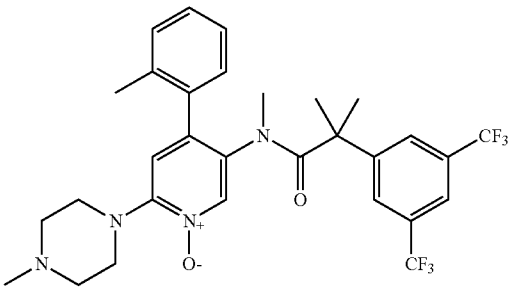
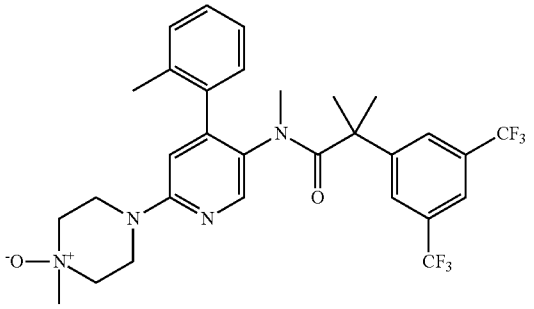
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

GA5



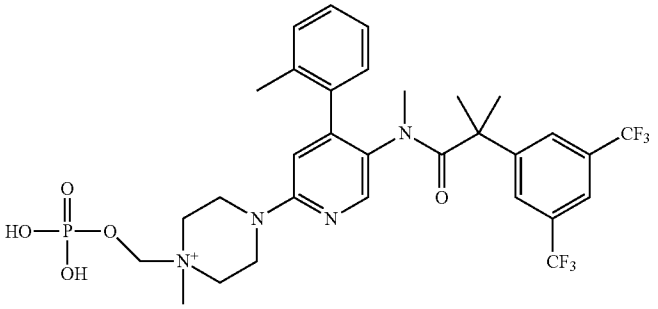
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

-continued

GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

or a pharmaceutically acceptable salt or adduct thereof.

In a further embodiment the invention is a compound of formula GA1,

formula GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium

or a pharmaceutically acceptable salt or adduct thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** reproduces stability data for various salts of 4-(5-(2-(3,5-bis(trifluoro-methyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphornooxy)methyl)piperazin-1-ium.

DETAILED DESCRIPTION

Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood

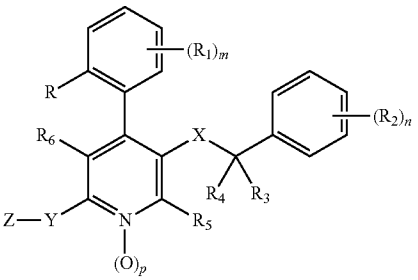
that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

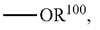
X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alkyl$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

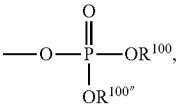
Z is a structural formula selected from the group consisting of:

(Ia)

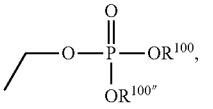
(Ib)



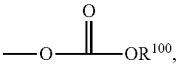
(Ic)



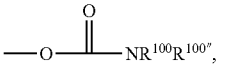
(Id)



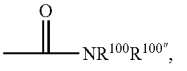
(Ie)



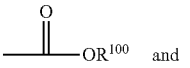
(If)



(Ig)

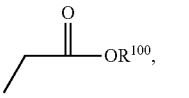


(Ih)



and

(Ii)



where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the

atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

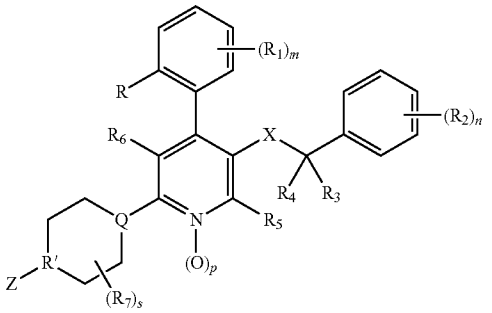
R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is from 0 to 4; n is from 0 to 5; p is from 0 to 1; and with a proviso that if a non-pyridine N-Oxide ($N^- \rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein X is —$NR^{101}C$(O). In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

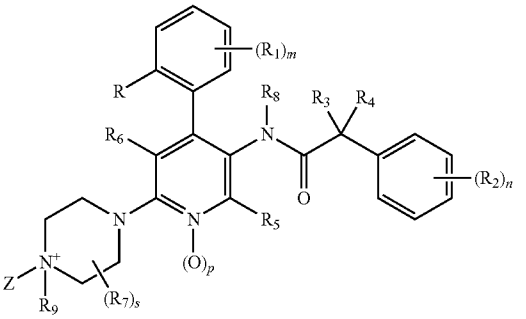
Formula (II)



where Q and R' are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

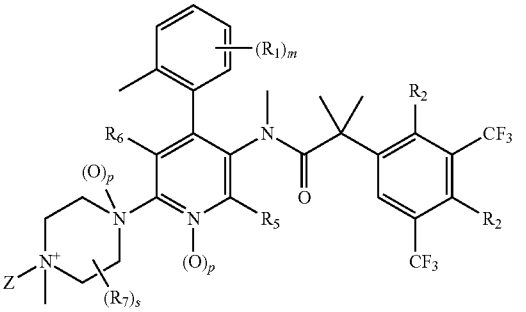
Formula (III)



where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

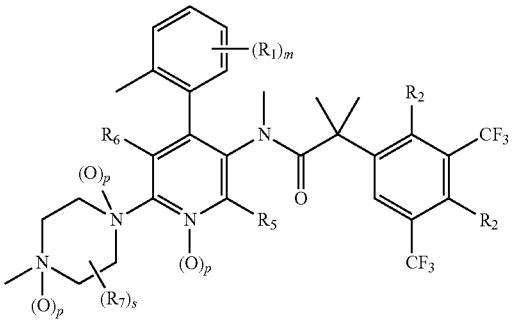
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

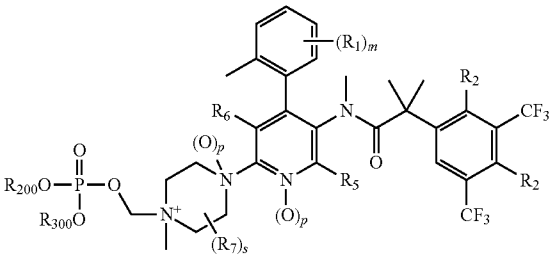
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

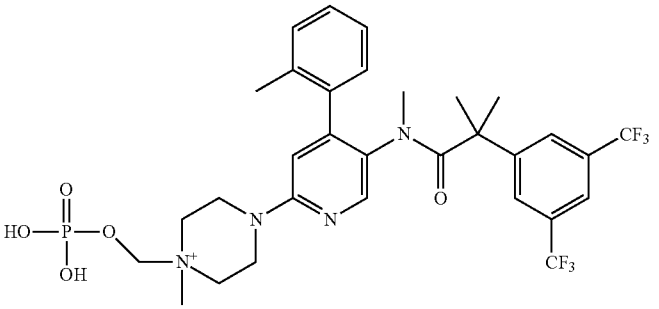
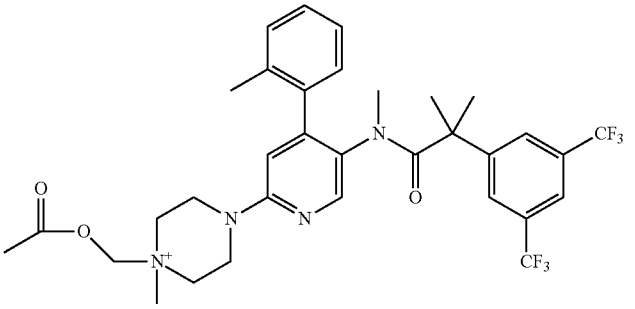
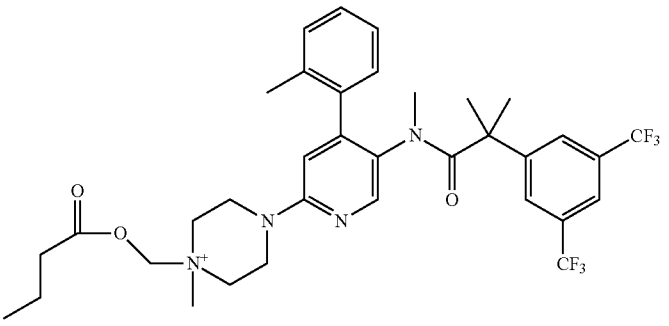
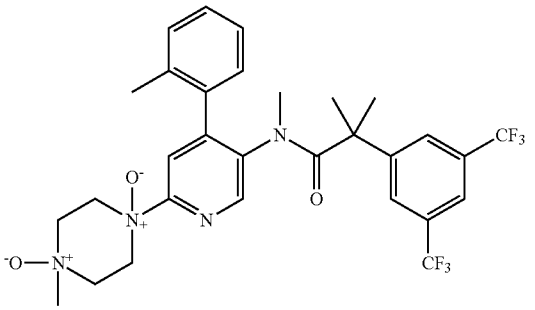
In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (VI):

Formula (VI)

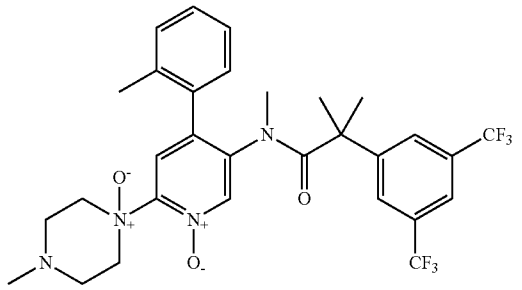
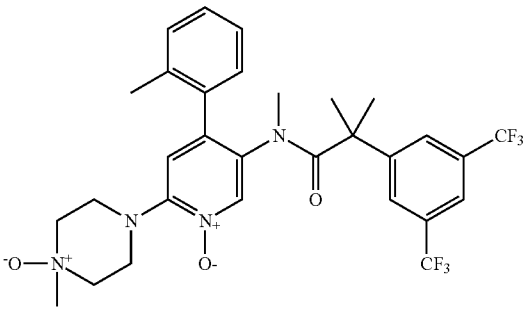
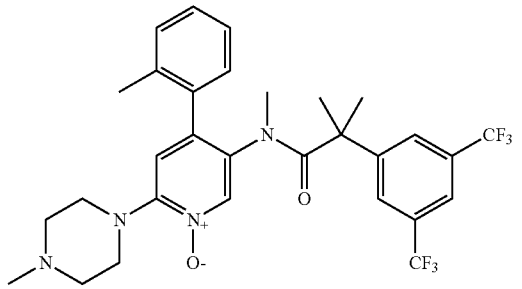
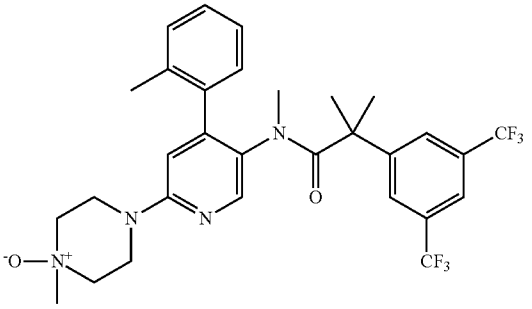


where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

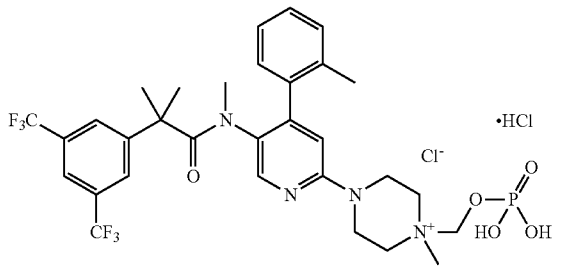
In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of:

GA1		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl)-1-((phosphonooxy)methyl) piperazin-1-ium,
GA2		1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,
GA3		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,
GA4		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

-continued

GA5		1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,
GA6		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide,
GA7		5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and
GA8		4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

A particular preferred compound is the chloride hydrochloride HCl salt of GA1 having the following chemical structure which, it has been found, is tremendously resistant to decoupling of the oxo-phosphonomethyl, and reversion of the active moiety to its parent state.



Salts and Adducts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced storage stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is

generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, (3-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

The disclosed compositions and compounds can be used in the form of adducts derived by formation of Lewis pairs, covalently linked adducts e.g. between N atoms and carbonyl-containing reactants, hydrates and alcoholates, host-guest adducts containing molecular species not bonded or associated with the medicinal compound, and other clathrates.

Depending on the particular compound, an adduct of the compound can be advantageous due to one or more of the adduct's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, an adduct of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where an adduct is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the adduct preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable adduct" refers to an adduct prepared by combining a compound, such as the disclosed compounds, with a gas, water, solvent, Lewis base, carbonyl-containing molecule, or guest molecule that is generally considered suitable for human consumption. Pharmaceutically acceptable addition species are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the adducts of the disclosed compounds are non-toxic "pharmaceutically acceptable adducts." Adducts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic adducts of the disclosed compounds which are generally prepared by reacting a compound of the invention with a suitable organic or inorganic addition species.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, include those derived from Lewis bases such as boric acid, aluminum hydroxide, organic sulfoxides, organic sulfones, organic sulfonium salts, H_3PO_3, siloxanes, and other Lewis bases.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from covalent bonding between an oxygen, nitrogen or sulfur atom of the compound and carbon dioxide, low alkyl aldehyde or ketone, vanillin, amino acid, or a nucleic acid.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from inclusion of an unbonded gas such as dioxygen, dinitrogen, carbon dioxide, nitrous oxide, ethyl ether, or other gas, contained within but not bonded to a crystalline or amorphous phase of the compound.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from association of a molecule of the compound with water, a pharmaceutically acceptable lower alkyl alcohol, or another pharmaceutically acceptable solvent that is associated in a molecular ratio with the compound.

In one embodiment the adduct is optionally a clathrate.

General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of

Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

The invention further provides methods for making suitable prodrugs of the 4-phenyl-pyridine derivatives. In one embodiment the invention provides a one-step, acid-free synthesis for functionalizing tertiary amines by reaction with chloromethyl dialkyl phosphate esters to create (phosphooxy)methyl prodrugs that are substrates for phosphatase enzymes. By contrast the prior art had required multiple synthetic steps for comparable reactions, including requiring the use of proton scavengers during initial reaction and requiring strong acid to deprotect the phosphate group in another step. In another embodiment the invention provides methods for making chloromethyl dialkyl phosphate esters having suitable purity and economy, because the quality of phosphate ester compositions from commercial sources is too low to provide acceptable yields for reactions according to the invention. In an additional embodiment the invention provides a method to stabilize the (phosphooxy)methyl prodrugs according to the invention by combination with two equivalents of hydrochloric acid, because whereas the prior art preferred the use of dibasic salts of (phosphooxy) methyl substituents for quaternary ammonium salts in prodrugs, the present invention had found that such salts are unstable and reform the underlying drug during storage.

Definition of Terms

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms. In one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y—," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X-Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile") —CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The term "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula —$NH(CH_3)$), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to =O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to =S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxido" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane, thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl

group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2—. The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2—. The term "methylenoxy" refers to the group —CH_2—O—. The term "methylenethioxy" refers to the group —CH_2—S—. The term "methylenamino" refers to the group —CH_2—N(H)—. The term "ethylenoxy" refers to the group —CH_2—CH_2—O—. The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule. If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active com-

pounds and compositions, for example, can be administered orally, rectally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

In some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods

of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide ≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg. orally on day 1, followed by 8 mg. orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously administered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-day course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a $5\text{-}HT_3$ antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said $5\text{-}HT_3$ antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said $5\text{-}HT_3$ antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg,

or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 mL.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodiment, the netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease.

In some other forms, disclosed are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

More Definitions of Terms

1. A, an, the

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes not only single carriers but also mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. In order to more fully document the state of the art to which this invention pertains, the disclosures of these publications are to be considered as being referenced individually, specifically and in their entireties for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

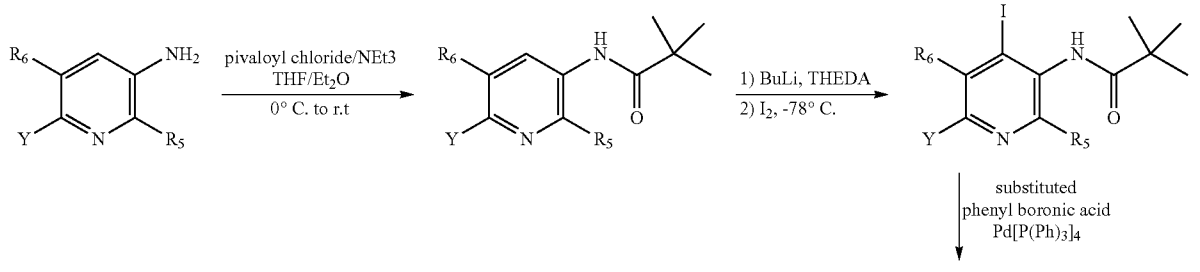
Example 1

Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

General Scheme of Preparing Compounds of Formula (I)

Scheme 1



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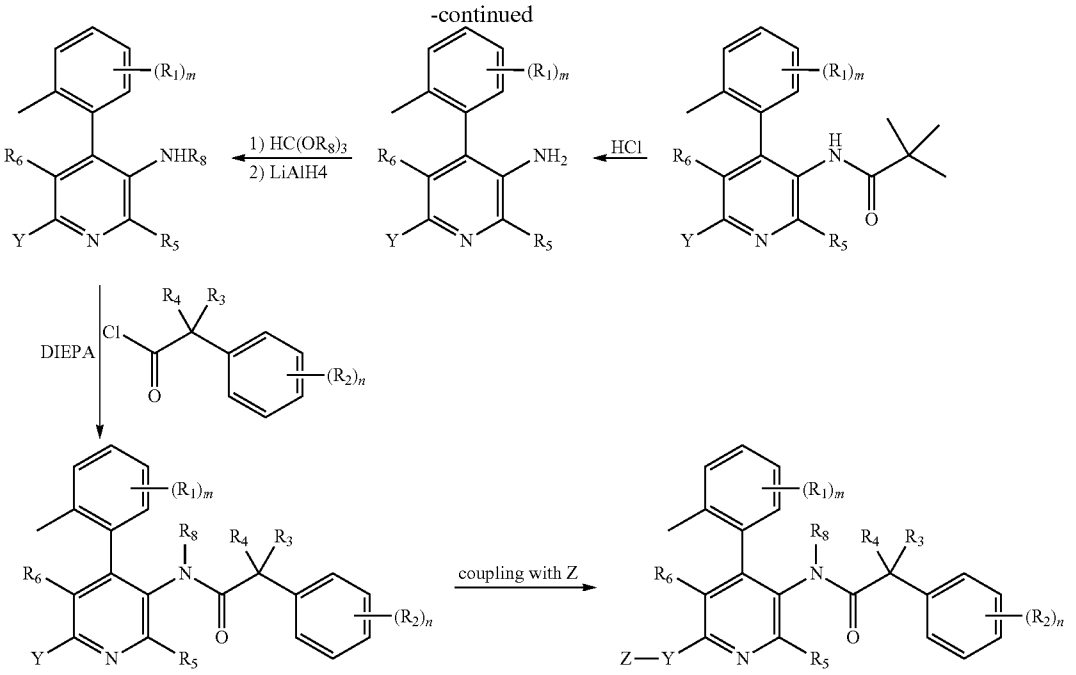
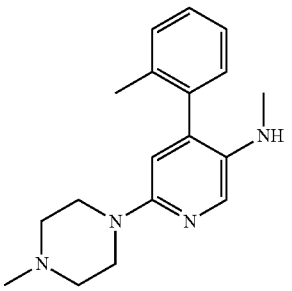


Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, which are referenced individually, specifically and in their entireties for the material contained in them that is relevant to the preparation of intermediate I.

Synthesis of methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THF were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolyl-magnesium chloride solution (1M in THF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THF removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent: ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution. The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THF were added 3.1 ml (42.0 mMol) thionylchloride and 143.mu.1 (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0° C. After 30 minutes at 0° C., THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as a beige crystalline foam. MS (ISP): 247 ($M+H^+$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamide in 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam. MS (ISP): 311 ($M+H^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol 4:1) to yield 100 mg (70%) 6-(4-methyl-

piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 ($M+H^+$, 100), 226 (42).

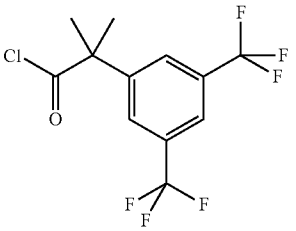
Step 5:

2.15 ml (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH=8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam. MS (ISP): 341 ($M+H^+$, 100), 284 (35).

Step 6:

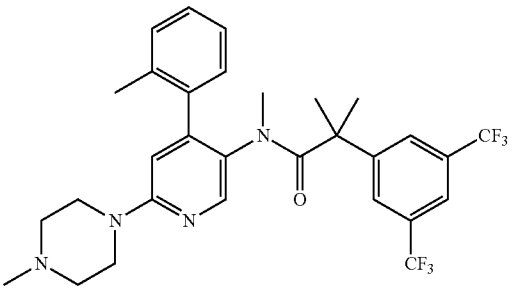
A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-Al® (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 ($M+H^+$, 100).

Synthesis of 2-(3,5-bis-Trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution was rotary evaporated to dryness. 9 ml Toluene were added and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, $3H_{arom}$); 1.77 (s, 6H, 2 CH_3).

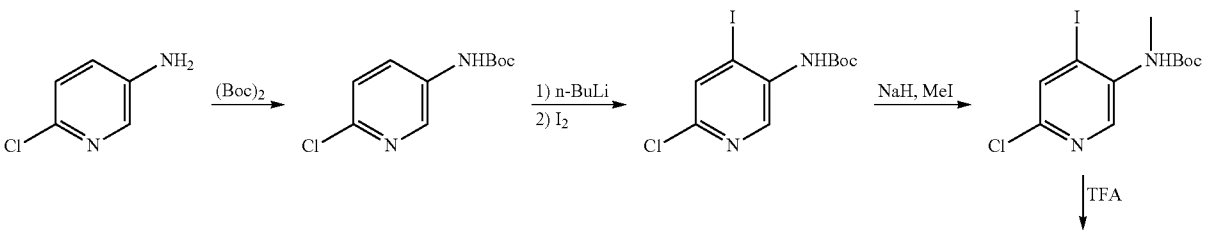
Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)



A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide as white crystals. M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2



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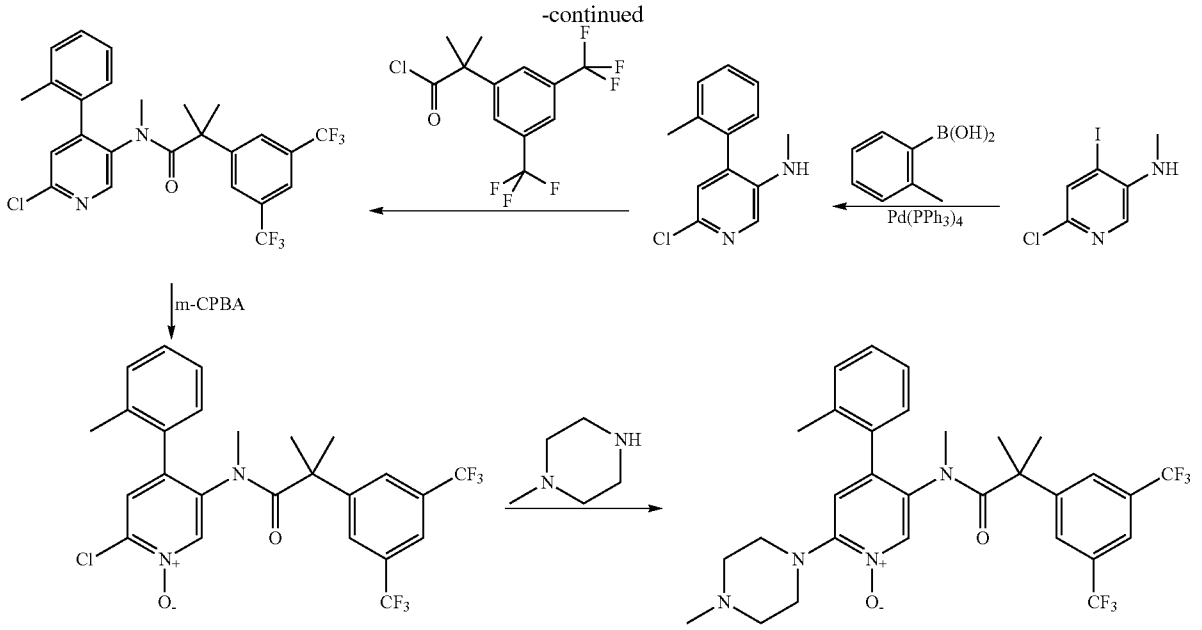


Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl (6-chloropyridin-3-yl) carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl (6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THF was added n-BuLi (600 mL, 1.5 mol) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THF was added. Then the solution was stirred at −78° C. for 4 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl (6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 mL of anhydrous THF was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THF was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl (6-chloro-4-iodopyridin-3-yl)(methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 mL of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol). The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under N_2 atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature. 1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,

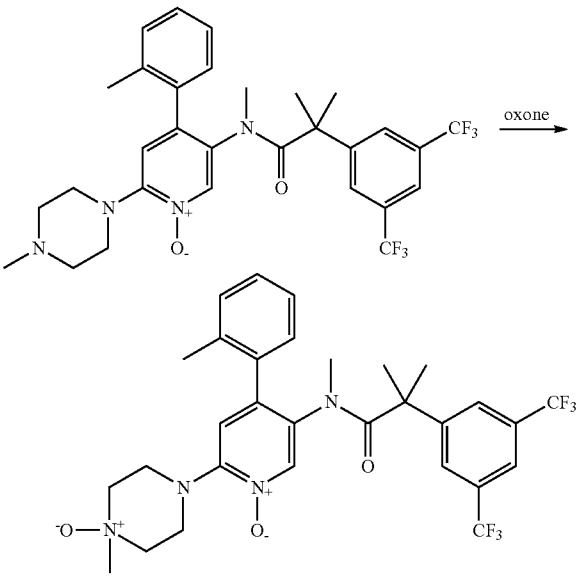
5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45-1.20 (m, 6H).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide

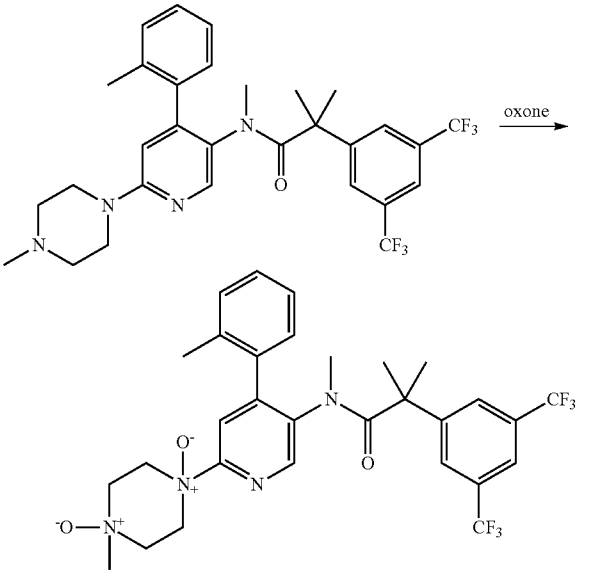
Scheme 3



To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 mL of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for 4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37-7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 2H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

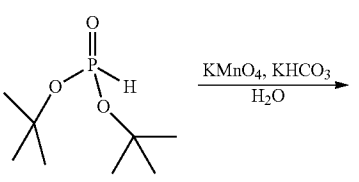
Scheme 4



To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (3.38 g, 40.3 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR (CDCl3, 400 MHz, at 333K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26-7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

Synthesis (A) of di-tert-butyl (chloromethyl) phosphate

Scheme 5



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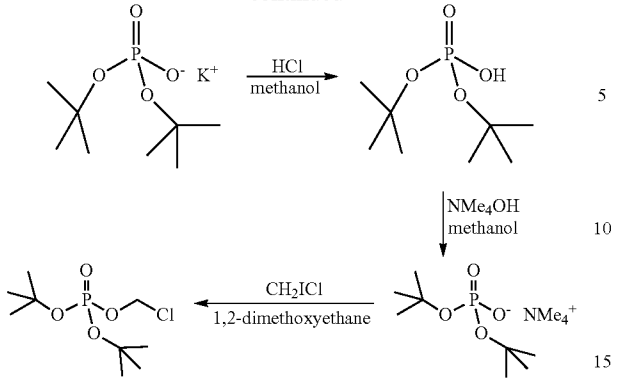

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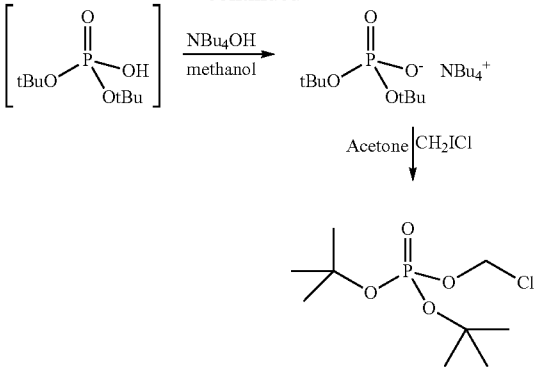
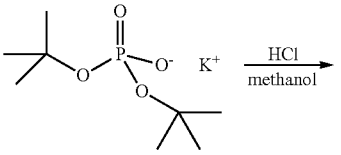


Di-tert-butyl phospohite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time. The reaction as then allowed to continue at room temperature for an additional half hour. Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the crude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloroiodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium without further purifications (60% yield): ^{1H}NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Synthesis (B) of di-tert-butyl (chloromethyl) phosphate

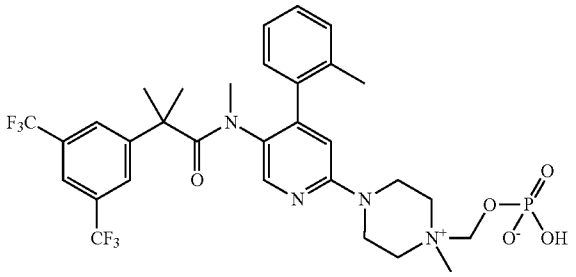
Scheme 5A



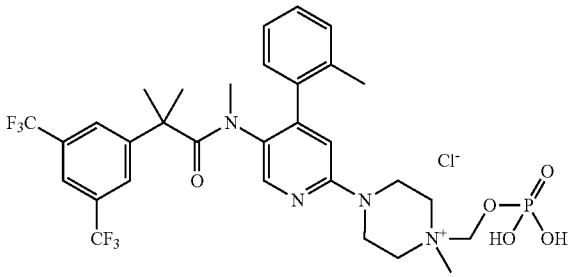
Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) is dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetrabuthylammonium hydroxide 1 M in methanol (20.14 mmole) while keeping the reaction cooled at 0° C. with efficient stirring. The resulting clear solution is placed under reduced pressure to give the intermediate product. The tetrabuthylammonium di-tert-butyl-phosphate dissolved in acetone is then added dropwise to 53.3 grams of chloroiodomethane (302.1 mmole) and stirred at 40° C. for 1-2 hours. The solvent and excess of chloroiodomethane are distilled off, the reaction mass suspended in TBME and then filtered. The filtrate is washed by a saturated solution of sodium bicarbonate and water and then placed under reduced pressure to substitute the solvent by acetone, i.e., to remove the solvent after which it is replaced with acetone. The chloromethyl di-tert-butyl phosphate 7-20% in acetone is used in the next step without further purifications (70-80% yield): ^{1}H-NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Stability Studies of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium salts

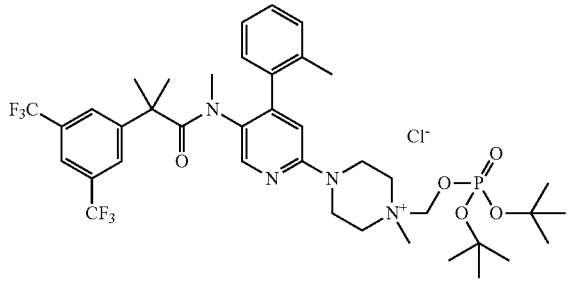
In order to further improve the stability and solubility of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium, a variety of its derivative salts were synthesized and tested. Their synthesis employed either a) neutralization of the dried diacid phosphate species and its corresponding base salts or b) a direct acid deprotection starting from the dried di(tert-butyl)-protected phosphate species. Neutralization was performed with L-histidine, magnesium salt, N-methyl-D-glucamine (dimeglumine), and L-lysine. Both procedures were tried in the synthesis of citric derivatives whereas with other acids the direct deprotection reaction was used. The FIGURES below show the most relevant structures.



Parent acid species

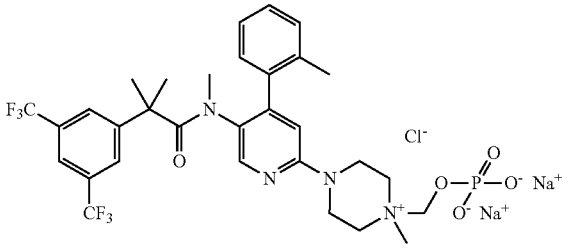


Diacid phosphate species

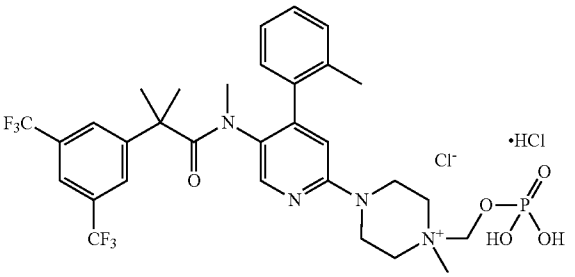


Protected phosphate species

-continued



Dibasic phosphate species



Chloride hydrochloride species

When the parent acid species was not stored in dry condition it was found to undergo over 8% degradation in the first week and over 65% degradation in the first six months. When the dried parent acid species was held at 30° C. in air it underwent 0.05% degradation in the first 7 days and at total of 7.03% degradation in six months. When the dried parent acid species was held under argon at room temperature it underwent up to 0.13% degradation in the first 7 days but then was essentially stable for six months. Results for various derivative salts are shown in Table 1 below.

TABLE 1

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	L-Histidine, 2 eq.	26.6%	95.94%	Degradation: +0.70% in 6 days (in air) +0.46% in 6 days (in argon)
MeOH	$Mg(OH)_2$, 2 eq.	48.6%	94.11%	Degradation: +0.81% in 6 days (in air) +0.29% in 6 days (in argon)
MeOH + DCM, 1:1	Citric acid, 2 eq.	N.A.	94.40%	From protected species.
MeOH	1. HCl dioxane, 4 eq. 2. $Ca(OH)_2$	>90%	94.50%	From protected species.
MeOH	H_3PO_4, 85%, 2 eq.	>90%	98.81%	From protected species and retains 0.39% of that species.
MeOH	HBr, 48%, 4 eq.	84.6%	96.11%	From protected species. Product degrades rapidly.
MeOH + DCM, 1:4	CH_3SO_3H	N.A.	61.54%	From protected species. Product NOT stable: contains 32.45% decomposition species.
MeOH	NaH_2PO_4, 4 eq.	N.A.	n.d.	Only 1.27 of parent species formed. Poor reaction.
MeOH	N-methyl-D-glucamine (Meglumine), 2 eq.	N.A.	96.88%	Degradation: +0.87% in 6 days (in air) +1.52% in 11 days (in argon)
MeOH	N-methyl-D-glucamine (Meglumine), 1 eq.	>99%	97.42%	Degradation: +0.77% in 6 days (in air) +0.83% in 7 days (in argon)

TABLE 1-continued

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH + DCM, 5:2	1. NaOH, 3 eq 2. Citric acid, 1 eq.	96.5%	97.49%	Degradation: +0.09% in 2 days (in argon) +0.59% in 89 days (in argon)
MeOH + DCM, 5:2	1. NaOH, 3 eq. 2. Fumaric acid, 1 eq.	93.8%	97.46%	Degradation: +1.95% in 14 days (in air) +1.80% in 12 days (in argon)
MeOH	L-lysine, 1 eq.	>99%	97.62%	Degradation: +0.69% in 14 days (in air) +0.48% in 12 days (in argon)

A more comprehensive showing of stability results is given in FIG. **1**, where the horizontal axis represents number of days of testing and the vertical axis represents the mass percent of degradation. Alphabetical letters are used to denote data points on the graph that correspond to degradation percentage values over time for respective salts of the same parent compound as just described above and in Table 2 below. The drawn lines correspond to general trends over periods of days for the benchmark salt (the disodium salt) and for the few salts that manifested more desirable results than the disodium salt.

TABLE 2

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
a	2 Dimeglumine	Air
b	2 Dimeglumine	Argon
c	Dimeglumine	Air
d	Dimeglumine	Argon
e	Lysine	Air
f	Lysine	Argon
g	Fumarate	Air
h	Fumarate	Argon

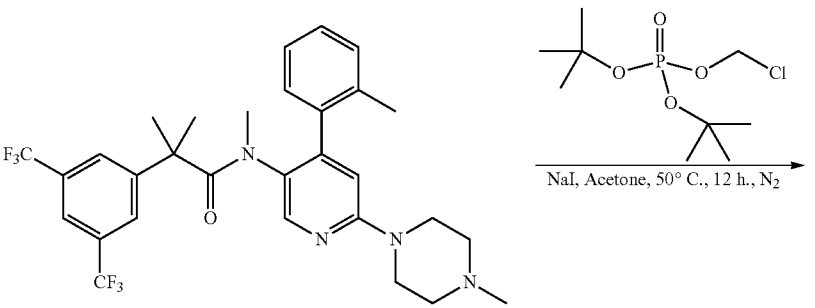
TABLE 2-continued

Identity Codes for Salts and Gases in FIG. 1.

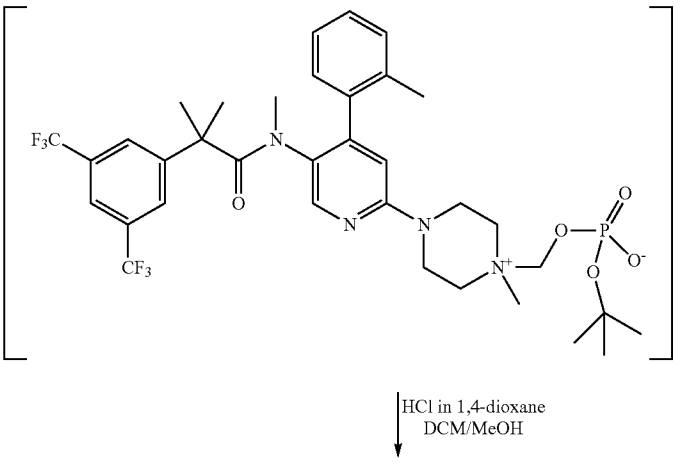
Letter Code	Salt	Ambient gas for storage
i	Citrate	Air
j	Citrate	Argon
k	Bromide	Air
l	Bromide	Argon
m	Mesylate	Nitrogen
n	Phosphate	Air
o	Phosphate	Argon
p	Citrate	Nitrogen
q	Calcium	Air
r	Calcium	Argon
s	Chloride hydrochloride, anhydrous	Air
t	Chloride hydrochloride, anhydrous	Argon
u	Disodium salt	Air
v	Histidine	Air
w	Histidine	Argon
x	Magnesium	Air
y	Magnesium	Argon

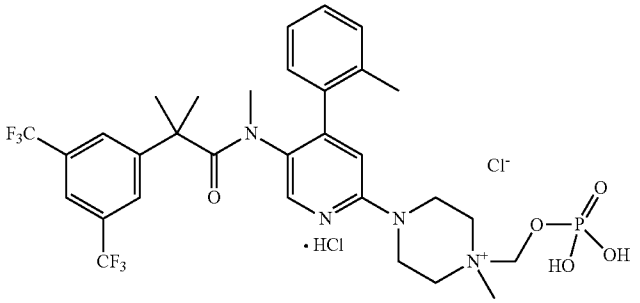
Synthesis (A) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

Scheme 6



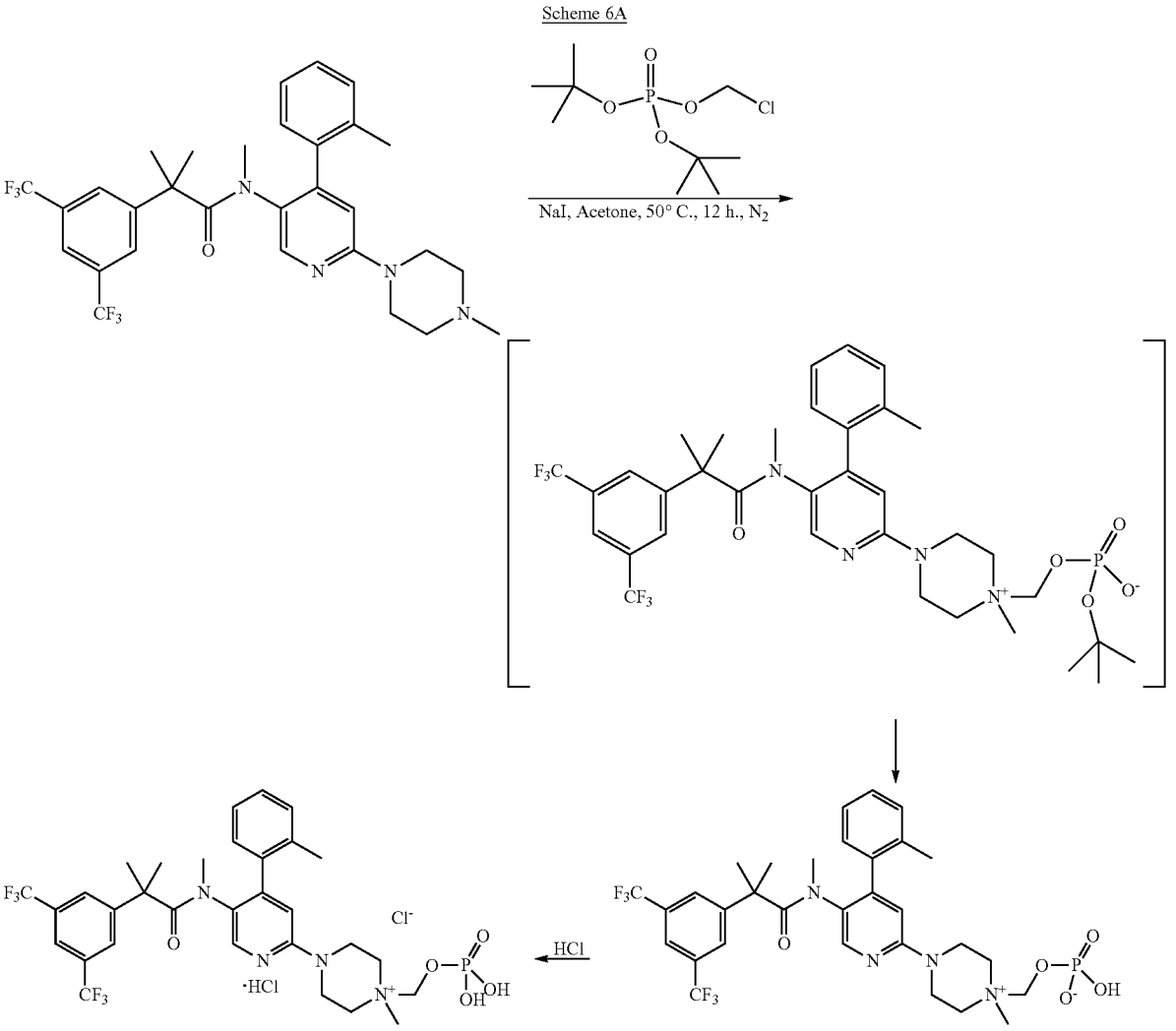
-continued





The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile. 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphtalene and 46.6 g (80.54 mmole) of 2-(3,5-bis (trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropylether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropylether/acetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-7.10 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m. 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis (trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl] oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride as white solid (Yield: 88-93%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

Synthesis (B) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride



To the solution of chloromethyl di-tert-butyl phosphate in Acetone (22.1 g from a 10% solution, 85.58 mmole), 15.5 g (103.24 mmole) of sodium iodide and 33.0 g (57.00 mmole) of netupitant were added and the solution heated at 50° C. for at 6-16 h. The precipitated salts were filtered off, the acetone distilled under reduced pressure and the crude product dissolved in 43.0 g of methanol and 43.0 g 1,4-dioxane. 12.6 g of HCl 4M in dioxane (113.85 mmole) were added, and then methanol is distilled off at 40° C. under reduced pressure. The solution is cooled at 5° C. and stirred at 5° C. for at least 2 h at 5° C. The product was isolated by filtration, purified by additional slurry in acetone (238 g), and filtered and washed with acetone (47 g) and pentane (2×72 g).

The product was finally dried under reduced pressure at 60° C. to afford 22-30 g of white-yellowish solid (Yield: 50-70%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J=8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

It is to be understood that the product shown in Scheme 6A is illustrative, being just one of several permutations in which the acidic protons bond to various atoms in an equilibrium. For instance depiction of other permutations would show a proton bound to one or more of the N atoms while one or more of the O atoms bound to the P atom would bear an anionic charge. The invention comprises all of the molecular species within that equilibrium and the product shown in the FIGURE is intended to represent all of them in a generic fashion.

7. Evaluation of Representative Compounds of Formula (I)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 3 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE 3

Chemical Stability and Solubility of Representative Compounds

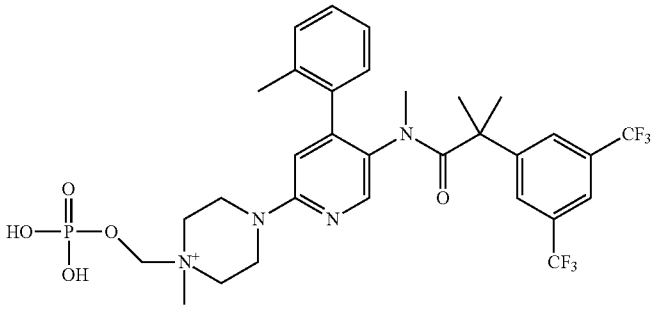
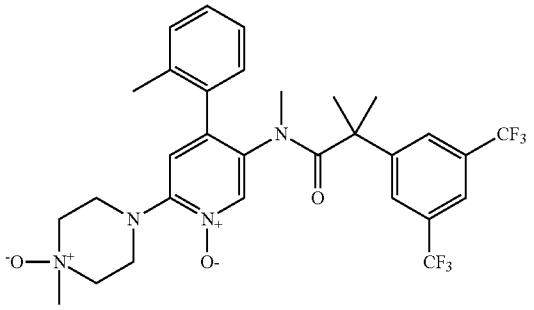
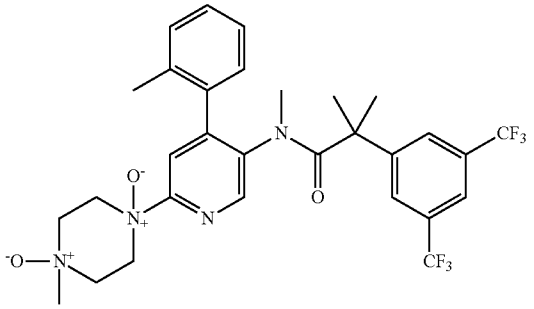
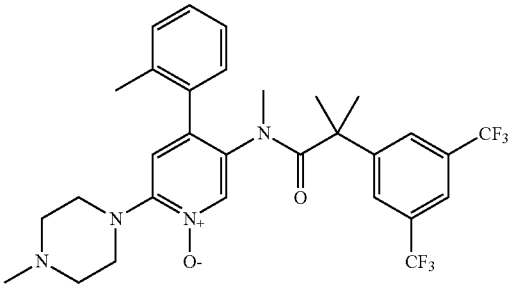
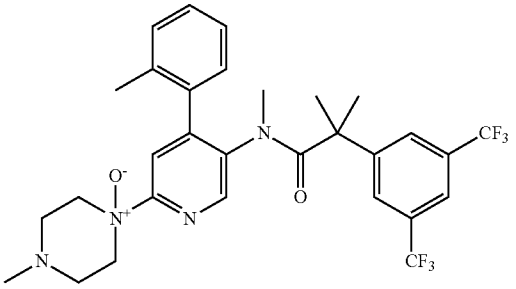
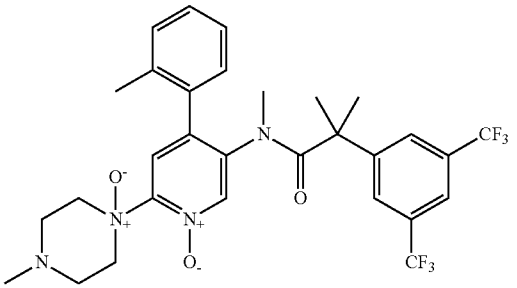
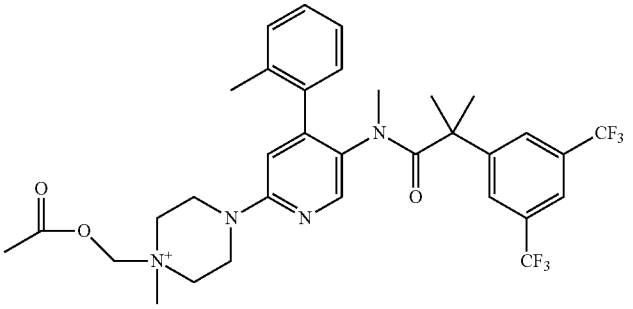
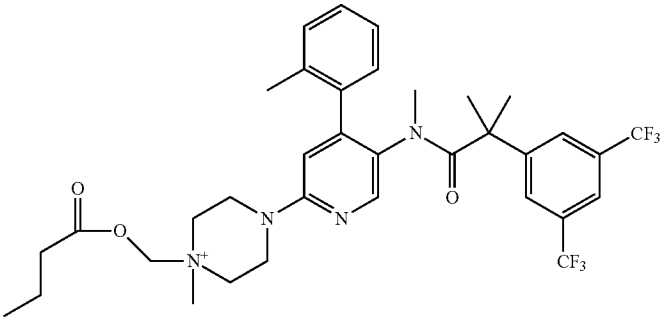
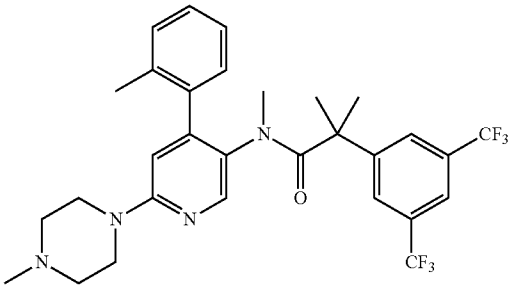
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1		medium	10-15 mg/ml
2		high	>10 mg/ml
3		high	>10 mg/ml
4		medium	~0.6 mg/ml
5*		medium	~1 mg/ml

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
6		low	N/A
7		low	insoluble
8		Low	insoluble
9*			0.25

*Reference Compound

ii. Local Tolerance

In contrast to netupitant (compound no. 9 in the above table), seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

There were minimal signs of inflammation at injection site and there was little edema;

No later stage thrombus was found in any animal studied;

Severity of inflammation was similar in compound and vehicle-treated animals;

No tissue necrosis was observed in any of the tails; and

The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 3), as compared to a reference compound—netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow

bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a dose volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Before administration, rats were fasted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pre-dose and at 0.05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO:Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solubility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (IV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, 15 and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC. MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 3, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 4:

TABLE 4

Comparative Bioequivalence Studies of Netupitant and Related Compounds

	IV			PO
	Compound 1	Compound 2	Compound 3	Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng · min/ml)	315627	88732	192730	307285
Bioequivalence (%)	103	29	63	

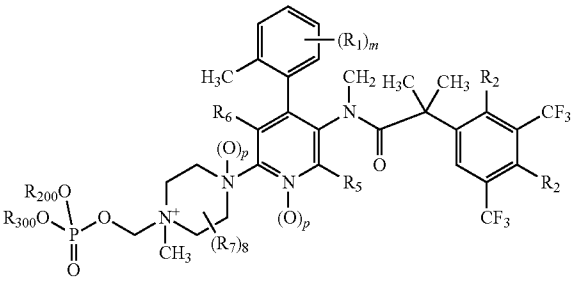
*Reference Compound

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby referenced individually and specifically for the material contained in them that is discussed in the sentence in which the reference is relied upon. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A compound of formula (VI):

(VI)



or a pharmaceutically acceptable salt thereof,

wherein:

each R_1 is independently hydrogen, halogen, alkyl, alkylNR^{101}R^{102}, alkenyl,—C(O)R^{101}, —C(O)NR^{101}R^{102}, —C(O)OR^{101}, —NR^{101}R^{102}, —NR^{101}C(O)R^{102}, —OR^{101}, —SR^{101}, —S(O)$_2$R^{102}, —S(O)$_2$NR^{101}R^{102}, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally substituted with one or more independently selected R^{103} substituents;

each R_2 is independently hydrogen, halogen, alkyl, alkyl$NR^{101}R^{102}$, alkenyl,—$C(O)R^{101}$, —$C(O)NR^{101}R^{102}$, —$C(O)OR^{101}$, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —OR^{101}, —SR^{101}, —$S(O)_2R^{102}$, —$S(O)_2NR^{101}R^{102}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally substituted with one or more independently selected R^{103} substituents;

R_5 is hydrogen, halogen, alkyl, alkyl$NR^{101}R^{102}$, alkenyl,—$C(O)R^{101}$, —$C(O)NR^{101}R^{102}$, —$C(O)OR^{101}$, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —OR^{101}, —SR^{101}, —$S(O)_2R^{102}$, —$S(O)_2NR^{101}R^{102}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally substituted with one or more independently selected R^{103} substituents;

R_6 is hydrogen, halogen, alkyl, alkyl$NR^{101}R^{102}$, alkenyl,—$C(O)R^{101}$, —$C(O)NR^{101}R^{102}$, —$C(O)OR^{101}$, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —OR^{101}, —SR^{101}, —$S(O)_2R^{102}$, —$S(O)_2NR^{101}R^{102}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally substituted with one or more independently selected R^{103} substituents;

each R_7 is independently hydrogen, halogen, alkyl, alkenyl, amino, —OR^{104}, or cycloalkyl, wherein the alkyl, alkenyl, amino and cycloalkyl are each optionally substituted with one or more independently selected R^{103} substituents;

R_{200} is hydrogen, alkyl, or cycloalkyl, wherein the alkyl and cycloalkyl are each optionally substituted with one or more independently selected R^{103} substituents;

R_{300} is hydrogen, alkyl, or cycloalkyl, wherein the alkyl and cycloalkyl are each optionally substituted with one or more independently selected R^{103} substituents;

R^{101} is hydrogen, halogen, cyano, nitro, oxide, alkyl, alkenyl, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$C(O)OR^{104}$, —$NR^{104}R^{105}$, —$NR^{104}C(O)R^{105}$, —$NR^{104}S(O)_2R^{105}$, —OR^{104}, —SR^{104}, —$S(O)_2NR^{104}R^{105}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally substituted with one or more independently selected R^{103} substituents;

R^{102} is hydrogen, halogen, cyano, nitro, oxide, alkyl, alkenyl, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$C(O)OR^{104}$, —$NR^{104}R^{105}$, —$NR^{104}C(O)R^{105}$, —$NR^{104}S(O)_2R^{105}$, —OR^{104}, —SR^{104}, —$S(O)_2NR^{104}R^{105}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are each optionally substituted with one or more independently selected R^{103} substituents; or

$R^{101}$and R^{102}, together with the atoms to which they are attached, form a fused or non-fused monocyclic, bicyclic or tricyclic carbocyclic or heterocyclic ring, which is optionally and independently substituted with one or more independently selected R^{103} substituents;

each R^{103} is independently halogen, cyano, nitro, oxide, alkyl, alkenyl, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$C(O)OR^{104}$, —$NR^{104}R^{105}$, —$NR^{104}C(O)R^{105}$, —$NR^{104}S(O)_2R^{105}$, —OR^{104}, —SR^{104}, —$S(O)_2NR^{104}R^{105}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{104} is hydrogen, halogen, cyano, nitro, oxide, alkyl, hydroxyalkyl, alkoxyalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, alkenyl, amino, hydroxy, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{105} is hydrogen, halogen, cyano, nitro, oxide, alkyl, hydroxyalkyl, alkoxyalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, alkenyl, amino, hydroxy, alkoxy, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

m is 0, 1, 2, 3, or 4;

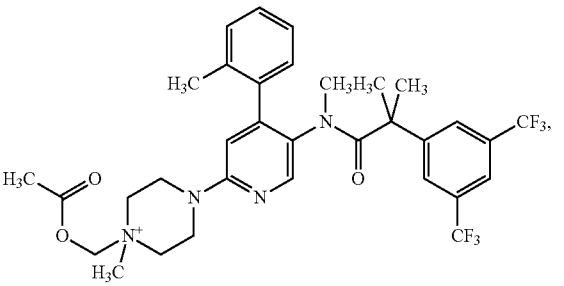
each p is independently 0 or 1; and

s is 0, 1, 2, 3, or 4;

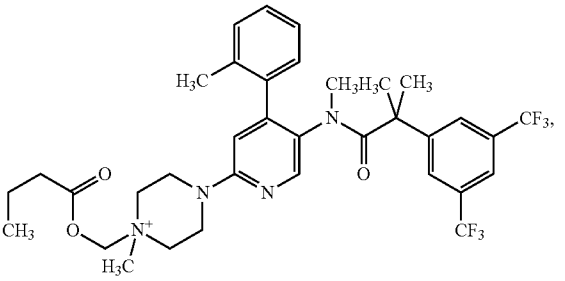
with a proviso that if a non-pyridine N-Oxide is present on the compound of formula (VI), then the total number of N-Oxides on the compound of formula (VI) is greater than one.

2. A compound selected from the group consisting of:

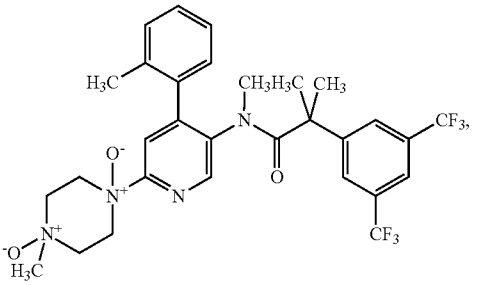
GA2



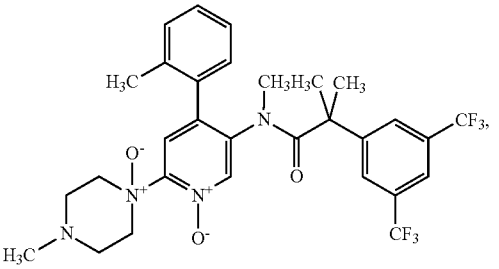
GA3



GA4

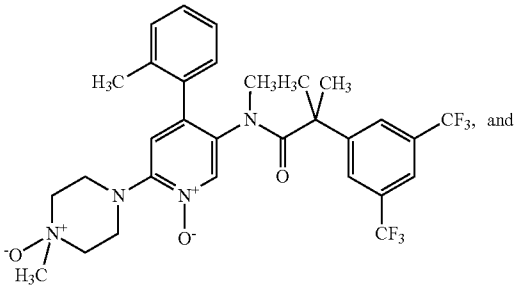


GA5

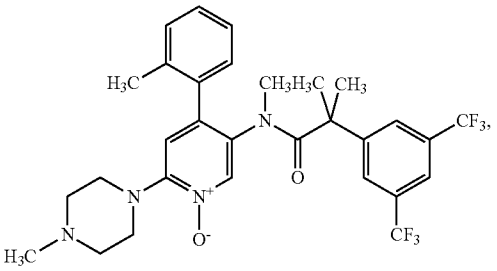


-continued

GA6



GA7



or a pharmaceutically acceptable salt thereof.

* * * * *

Exhibit I

US010828297B2

(12) **United States Patent**
Trento et al.

(10) **Patent No.: US 10,828,297 B2**
(45) **Date of Patent: *Nov. 10, 2020**

(54) **COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING**

(71) Applicant: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH)

(72) Inventors: **Fabio Trento**, Pare (IT); **Sergio Cantoreggi**, Cagiallo (CH); **Giorgia Rossi**, Cernobbio (IT); **Roberta Cannella**, Varese (IT); **Daniele Bonadeo**, Casalzuigno (IT)

(73) Assignee: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 29 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/923,050**

(22) Filed: **Mar. 16, 2018**

(65) **Prior Publication Data**

US 2018/0256567 A1 Sep. 13, 2018

Related U.S. Application Data

(63) Continuation of application No. 15/003,327, filed on Jan. 21, 2016, now Pat. No. 9,943,515, which is a continuation of application No. 14/069,970, filed on Nov. 1, 2013, now Pat. No. 9,271,975, which is a continuation of application No. 13/077,462, filed on Mar. 31, 2011, now Pat. No. 8,623,826, which is a continuation of application No. PCT/IB2010/003106, filed on Nov. 18, 2010.

(60) Provisional application No. 61/262,470, filed on Nov. 18, 2009, provisional application No. 61/382,709, filed on Sep. 14, 2010.

(51) **Int. Cl.**

A61K 31/496	(2006.01)
A61K 9/48	(2006.01)
A61K 31/4178	(2006.01)
A61K 31/473	(2006.01)
A61K 31/573	(2006.01)
A61K 45/06	(2006.01)
A61K 9/20	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/496*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 9/4808*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 31/4178*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 45/06*** (2013.01); *Y10S 514/872* (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/573; A61K 31/4178
USPC 514/17.7
See application file for complete search history.

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(Continued)

Primary Examiner — Walter E Webb
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan

(57) **ABSTRACT**

Provided are compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

23 Claims, 5 Drawing Sheets

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Exhibit D11: Steven M. Grunberg et al., "Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial" published on May 11, 2009; 10 pages.
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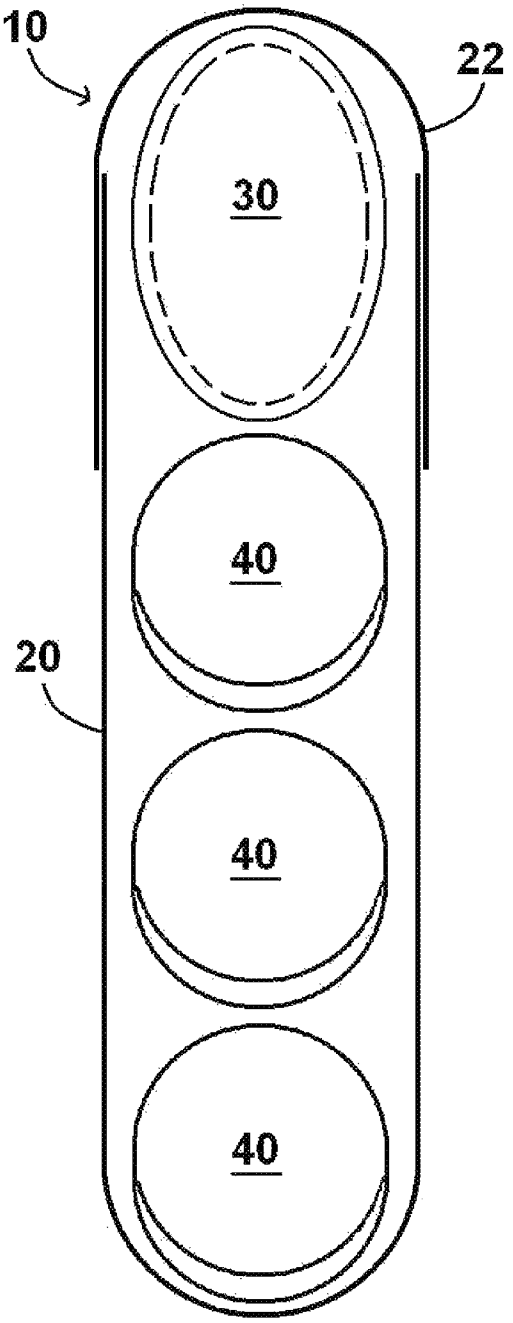


Figure 1

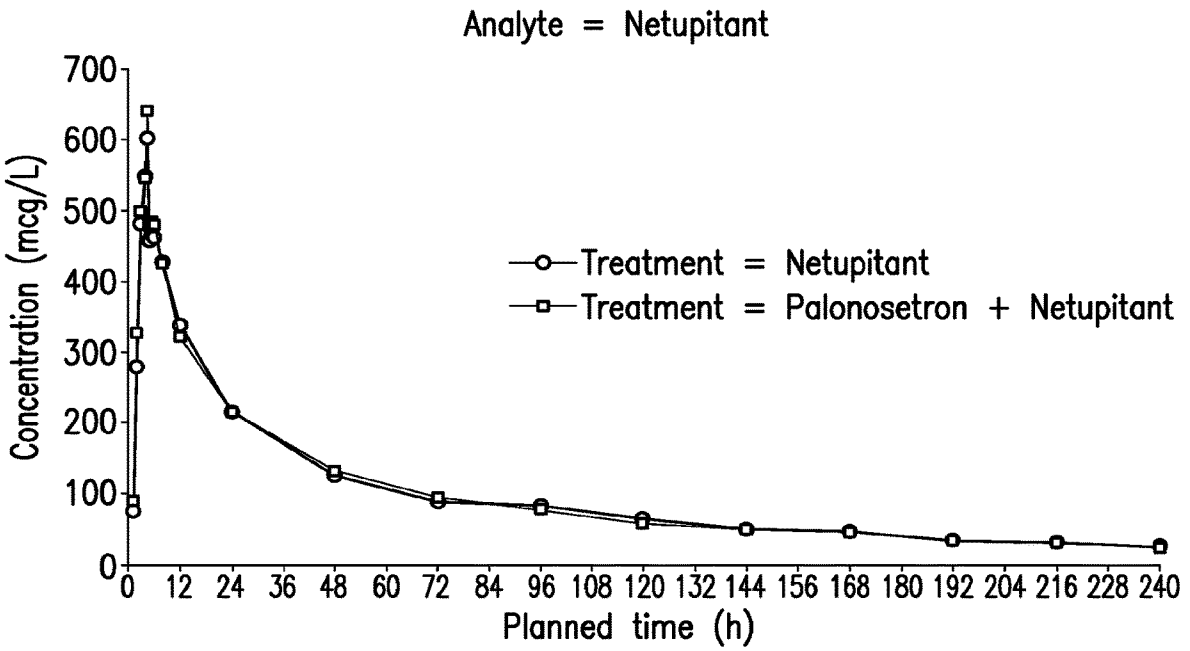

Analyte = Netupitant
Concentration (mcg/L)
700
600
500
400
300
200
100
0
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240
Planned time (h)
Treatment = Netupitant
Treatment = Palonosetron + Netupitant

FIG.2

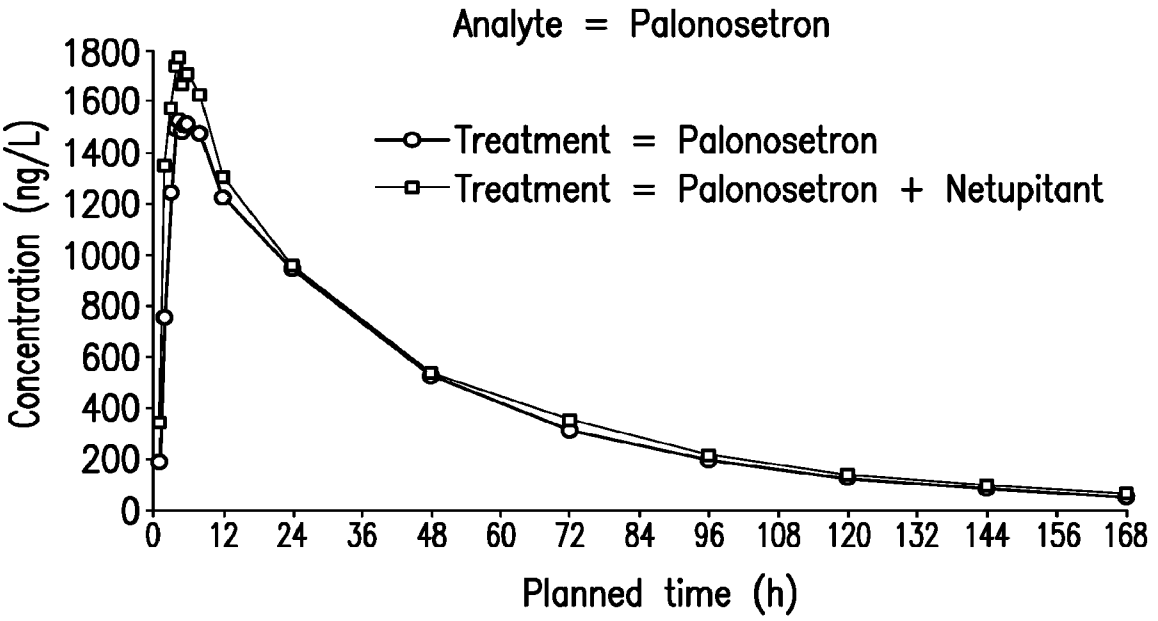

Analyte = Palonosetron
Treatment = Palonosetron
Treatment = Palonosetron + Netupitant
Concentration (ng/L)
1800
1600
1400
1200
1000
800
600
400
200
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Planned time (h)

FIG.3

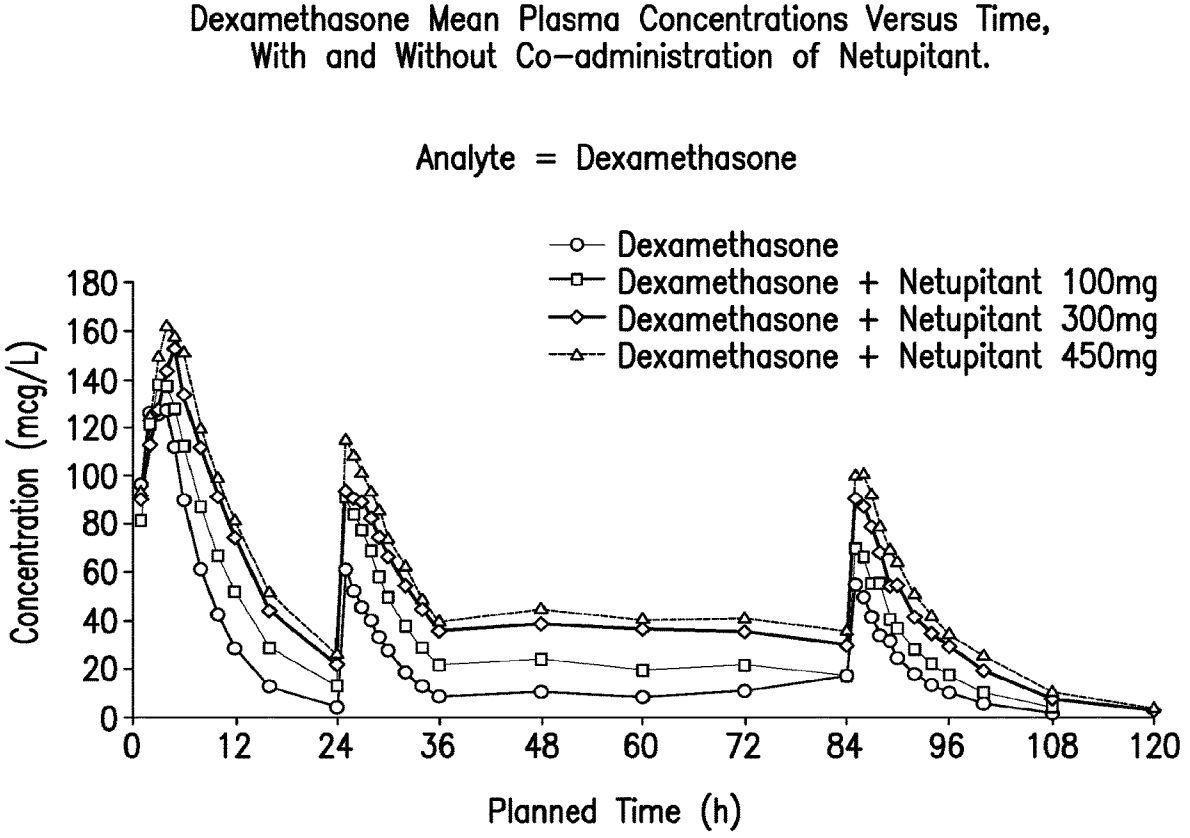

Dexamethasone Mean Plasma Concentrations Versus Time,
With and Without Co-administration of Netupitant.
Analyte = Dexamethasone
Dexamethasone
Dexamethasone + Netupitant 100mg
Dexamethasone + Netupitant 300mg
Dexamethasone + Netupitant 450mg
Concentration (mcg/L)
180
160
140
120
100
80
60
40
20
0
0
12
24
36
48
60
72
84
96
108
120
Planned Time (h)

FIG.4

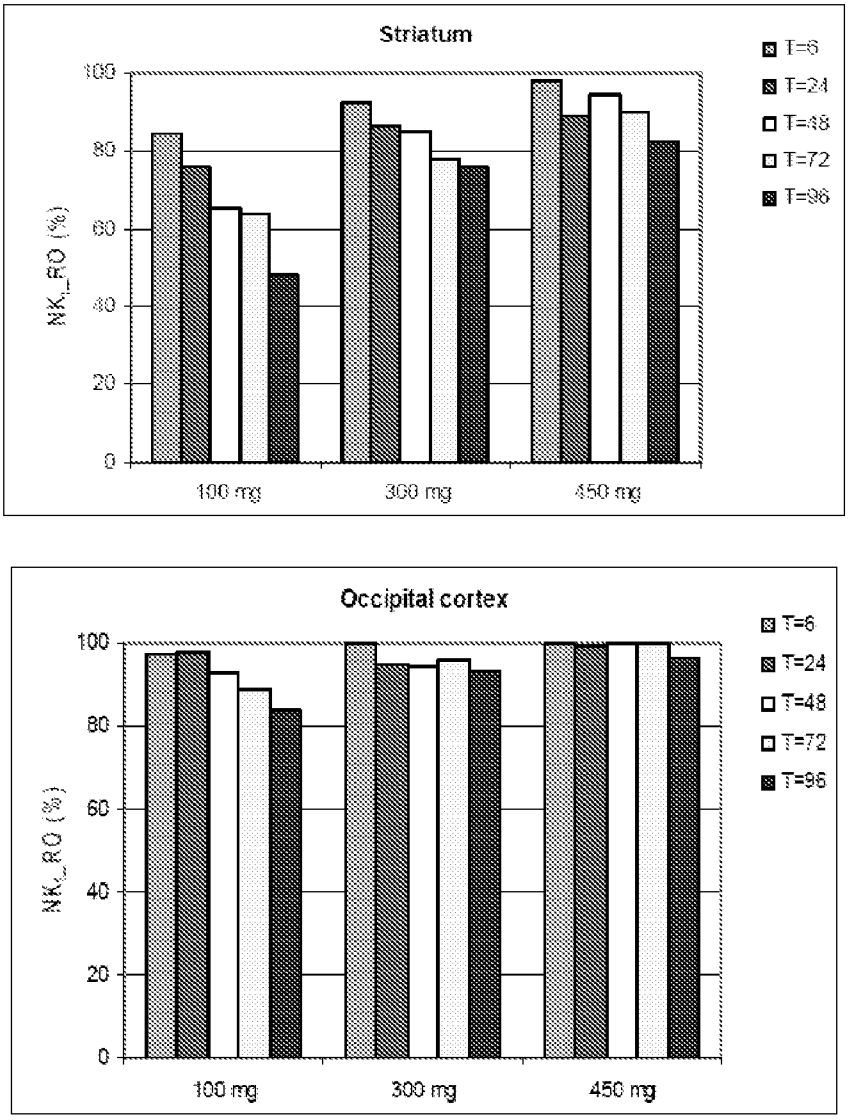

Striatum
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96
Occipital cortex
NK_RO (%)
100
80
60
40
20
0
100 mg
300 mg
450 mg
T=6
T=24
T=48
T=72
T=96

FIG. 5

COMPOSITIONS AND METHODS FOR TREATING CENTRALLY MEDIATED NAUSEA AND VOMITING

FIELD OF THE INVENTION

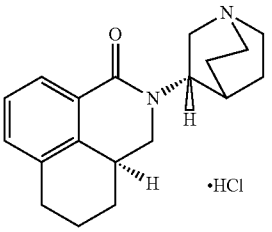
The present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.

BACKGROUND OF THE INVENTION

With the development of the 5-HT_3 antagonist in the early 1990s, there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare. Palonosetron hydrochloride is sold in the United States as a sterile injectable liquid under the ALOXI® brand, in sterile unit dose vials containing 0.075 or 0.25 mg. of palonosetron hydrochloride. Palonosetron hydrochloride also is also sold as an orally administered soft-gel dosage form containing 0.5 mg. of palonosetron hydrochloride.

The official chemical name for palonosetron hydrochloride is (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hberiz [de]isoquinoline hydrochloride (CAS No. 119904-90-4); its empirical formula is $C_{19}H_{24}N_2O.HCl$, and its molecular weight is 332.87. The compound is represented by the following chemical structure:

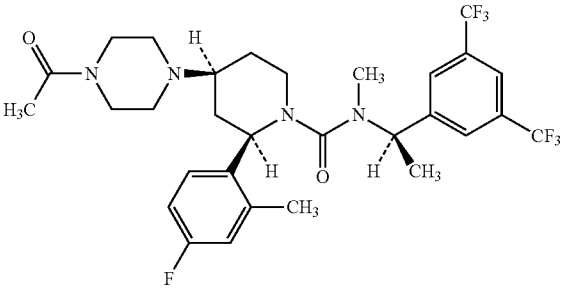


Methods of synthesizing palonosetron are described in U.S. Pat. Nos. 5,202,333 and 5,510,486. Pharmaceutically acceptably dosage forms are described in PCT publications WO 2004/067005 and WO 2008/049552 from Helsinn Healthcare.

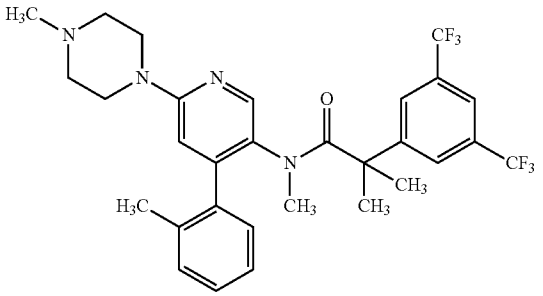
NK_1 antagonists have also recently emerged as a tool for combating nausea and vomiting from emetogenic medical procedures. Most recently, aprepitant was approved by the Food and Drug Administration ("FDA") for use in combination with other anti-emetic agents for the prevention of

nausea and vomiting from moderately and highly emetogenic chemotherapy. However, it quickly became apparent that aprepitant's effect was limited principally to vomiting—not nausea—and that aprepitant did not provide as much benefit during the acute phase of CINV. When tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to a 5-HT_3 antagonist alone. See FDA Approved Labeling for Emend®. Thus, while aprepitant is approved by FDA for the prevention of nausea and vomiting in humans, this indication is somewhat misleading because aprepitant did not reduce nausea in the clinical trials preformed for aprepitant more than nausea controlled by the other components of the anti-emetic regimen. In addition, the results reported in Grunberg et al., SUPPORT CANCER CARE (2009) 17:589-594, from a combined treatment of aprepitant and palonosetron, were far from promising.

Merck & Co. markets aprepitant, as EMEND® in the United States. The product is approved in a capsule dosage form, and is marketed for the prevention of CINV (acute and delayed) in combination with other anti-emetic agents such as ondansetron and metoclopramide. The product reportedly has a terminal half-life of from 9 to 13 hours. While aprepitant has demonstrated some effect against nausea, its effects have been inconsistent. Casopitant is another NK_1 antagonist that has been tested against nausea and vomiting in humans. A clinical study of casopitant is discussed in *Therapeutics and Clinical Risk Management* 2009:5 pp 375-384 to Ruhlmann et al. and *Drug Metabolism and Disposition*, vol. 37, No. 8, 2009, pp. 1635-1645 to Pellegatti et al. As reported by Ruhlmann et al. in THERAPEUTICS AND CLINICAL RISK MANAGEMENT, 2009:5 375-384, casopitant had no statistically significant effect against nausea when administered in response to moderately emetogenic chemotherapy, and even induced nausea as a side effect. Casopitant has the formula (2R,4S)-4-(4-acetytlpiperazin-1-yl)-N-{(1R)-1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide, and the below chemical structure:



Netupitant is another selective NK_1 receptor antagonist under development by Helsinn Healthcare, having the formula 2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethyl-N-[4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-yl]propanamide, or Benzeneacetamide, N,α,α-trimethyl-N-[4-(2-methylphenyl)-6-(4-methyl-1-piperazinyl)-3-pyridinyl]-3,5-bis(trifluoromethyl)-, and the below chemical structure:



Methods of synthesizing and formulating netupitant and its prodrugs are described in U.S. Pat. Nos. 6,297,375, 6,719,996 and 6,593,472 to Hoffmann La Roche.

Other representative NK_1 antagonists include ZD4974 (developed by AstraZeneca), CGP49823 (developed by Ciba-Geigy), Lanepitant and LY686017 (developed by Eli Lilly), FK888 (developed by Fujisawa), Vofopitant, Vestipitant and Orvepitant (developed by GlaxoSmithKline), Befetupitant (developed by Hoffmann-La Roche), R116031 (developed by Janssen), L-733060 and L-736281 (developed by Merck), TKA731, NKP608 and DNK333 (developed by Novartis), CP-96345, CP-99994, CP-122721, CJ-17493, CJ-11974 and CJ-11972 (developed by Pfizer), RP67580 and Dapitant (developed by Rhone-Poulenc Rorer), Nolpitantium and SSR240600 (developed by Sanofi-Aventis), SCH388714 and Rolapitant (developed by Schering-Plough), TAK637 (developed by Takeda), HSP117 (developed by Hisamitsu), KRP103 (developed by Kyorin Pharm) and SLV317 (developed by Solvay). Chemical structures of the above-mentioned NK_1 antagonists are shown below and discussion of those compounds as well as other NK_1 antagonists is present in *Expert Opin. Ther. Patents* (2010) 20(8), pp 1019-1045 by Huang et al.

The background of U.S. Pat. No. 6,297,375 suggests that NK_1 antagonists are useful for treating a variety of conditions in which substance P (the natural ligand for the NK_1 receptor) is active. These conditions include depression, pain (especially pain resulting from inflammatory conditions such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease), central nervous system (CNS) disorders such as Parkinson's disease and Alzheimer's disease, headache, anxiety, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases. The background even mentions motion sickness and vomiting, but fails to call out nausea specifically.

Accordingly, there is a need in the art for more effective treatments of nausea and vomiting, particularly nausea and vomiting emanating from chemotherapy, radiotherapy and surgery. In addition, given the prolonged incidence of nausea and vomiting induced by these emetic events, there is a need for treating such nausea and vomiting for a prolonged period of time. Further, there is a need for the development of dosage forms to reduce drug-drug interaction, improve stability, and potentiate effects of each component of the combined dosage forms.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the invention to provide new methods for treating or preventing nausea and vomiting using an NK_1 antagonist, particularly netupitant.

It is another object of the invention to provide methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

Still another object of the invention is to augment existing treatments for CINV, RINV or PONV by steroids and 5-HT_3 antagonists, and thereby provide additional protection against both nausea and vomiting, especially during the acute and delayed phases.

Another object of the invention is to provide a single combined dose of netupitant and a 5-HT_3 antagonist and to the use of that single dose without further dosing, for the treatment of nausea and vomiting during the acute and delayed phases of CINV, RINV or PONV.

It is another object to provide novel methods to treat nausea, vomiting, and other undesirable effects from moderately emetogenic and highly emetogenic chemotherapy ("MEC and HEC"), especially HEC, during the acute and delayed phases following such treatments.

It is another object to provide novel dosage forms to reduce drug-drug interaction, improve stability, enhance bioavailability and potentiate therapeutic effect of each component of the combined dosage forms comprising netupitant and/or 5-HT_3 antagonist and/or dexamethasone, in treating or preventing nausea and vomiting.

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

These discoveries have led to the development of a unique dosing regimen to treat nausea during the first day after an emesis-inducing event, in addition to the second, third, fourth and fifth days after such induction. Therefore, in one embodiment the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT_3 antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when palonosetron is in combi-

nation with netupitant as opposed to palonosetron in single dose administration. Based on these discoveries, solid oral dosage forms have been developed that combine netupitant or another NK1 antagonist and palonosetron for the treatment of acute and delayed emesis.

It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself). Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, consisting essentially of:

- Day 1 netupitant—administering to said patient on day one netupinant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective against nausea and vomiting during the acute and delayed phases, and which is effective to enter the systemic circulation, cross the blood brain barrier and occupy at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;
- Day 1 palonosetron—administering to said patient on day one a therapeutically effective amount of a $5\text{-}HT_3$ antagonist (preferably palonosetron) effective to treat said nausea and vomiting during the acute and delayed phases;
- Day 1 dexamethasone—administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and
- Days 2-5 dexamethasone—when the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

The dosage forms are extremely versatile and stable owing to their unique design and formulation. This versatility and stability is accomplished by formulating the NK1 antagonist and palonosetron in separate dosage forms and combining the dosage forms in one capsule. Thus, for example, the palonosetron can be formulated in a small gel-cap at a dose of around 0.5 mg, and the netupitant or other NK1 antagonist formulated in a tablet at a dose of about 100 to 150 mg. A capsule can then be filled with one or more palonosetron gel-caps and one or more netupitant (or other NK1 antagonist) tablets, depending on the therapeutic objective for the product. Because the palonosetron and NK1 antagonist are in separate dosage units, they can be formulated without regard to the stability of the other, and without degradation to by-products, for instance (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate, a degradation by-product of palonosetron. As a result, the presently discovered dosage forms offer advantages, such as, reducing drug-drug interaction, improving stability, and potentiating effects of each component of the dosage forms in treating or preventing emesis.

Thus, in one embodiment the invention provides an orally administered dosage form comprising a combination of palonosetron and an NK1 antagonist (preferably netupitant), or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides an orally administered capsule dosage form comprising (a) an outer shell; (b) one or more tablets housed within said outer shell, each comprising an NK1 antagonist (preferably netupitant) or a pharmaceutically acceptable salt or prodrug thereof and one or more pharmaceutically acceptable excipients; and (c) one or more soft-gel capsules housed within the outer shell, each comprising palonosetron or a pharmaceutically acceptable ester or prodrug thereof and one or more pharmaceutically acceptable excipients; wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo [de] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate in an amount that does not exceed 3 wt. %.

In still other embodiments the invention provides methods of treating acute and delayed-onset emesis by administering the dosage forms of the present invention to a human in need thereof, preferably shortly before the emesis inducing event.

Additional embodiments and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

FIG. **1** depicts a capsule containing one soft-gel capsule of palonosetron and three tablets of netupitant.

FIG. **2** is a two dimensional graph plotting the pharmacokinetic profile of netupitant in humans following oral administration of netupitant alone and netupitant together with palonosetron.

FIG. **3** is a two dimensional graph plotting the pharmacokinetic profile of palonosetron in humans following oral administration of palonosetron alone and palonosetron together with netupitant.

FIG. **4** is a two dimensional graph plotting mean plasma concentrations of dexamethasone over time following administration with and without netupitant.

FIG. **5** contains two bar graphs that depict the average NK_1 receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum and occipital cortex, as measured using positron emission topography.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following definitions and detailed description of preferred embodiments of the invention and the non-limiting Examples included therein.

Definitions and Use of Terms

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" or like terms as used herein means any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" or "ca." will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

As used herein, the term "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. In addition, the term "pharmaceutically acceptable salt" refers to a salt of a compound to be administered prepared from pharmaceutically acceptable non-toxic acids. Examples of suitable inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Suitable organic acids may be selected from aliphatic, aromatic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenyl acetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic (besylate), stearic, sulfanilic, alginic, galacturonic, and the like.

Pharmaceutically acceptable salts of palonosetron include palonosetron hydrochloride. Pharmaceutically acceptable pro-drugs of netupitant include those described in U.S. Pat. Nos. 6,593,472, 6,747,026 and 6,806,370, including the N-oxide of netupitant. The contents of these publications are incorporated herein by reference. When a molecule is referred to herein in its base or salt form, it will be understand also to encompass other pharmaceutically acceptable salt forms of the molecule.

As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.

The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

The terms "treating" and "treatment," when used herein, refer to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder.

As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

5-HT_3 antagonists include the various setrons such as, for example, palonosetron, ondansetron, dolasetron, tropisetron, and granisetron, and their pharmaceutically acceptable salts. A preferred 5-HT_3 antagonist is palonosetron, especially its hydrochloride salt.

"Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide >1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.

"Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible.

Methods of Treatment

As noted above, the invention is premised on several unique discoveries, and provides the following independent methods that can be practiced according to the present invention, including:

In a first principal embodiment, the invention provides a method of treating nausea and vomiting for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration.

In a second principal embodiment, the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

(i) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in an amount which is therapeutically effective to treat nausea and vomiting during the acute and delayed phases, which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of NK_1 receptors in the striatum seventy-two hours after said administration;

(ii) administering to said patient on day one a therapeutically effective amount of a 5-HT_3 antagonist (preferably palonosetron, more preferably 0.5 mg. of oral palonosetron as palonosetron hydrochloride) effective to treat said nausea and vomiting during the acute and delayed phases;

(iii) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant and palonosetron, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

(iv) if the patient is undergoing highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone on days two, three and four.

Various sub-embodiments are envisaged for these principal embodiments. For example, the netupitant can be administered as a free base or a pharmaceutically acceptable salt thereof, but is preferably administered as the free base. In addition, the netupitant is preferably administered in an amount ranging from about 50 to about 500 mg., from about 200 to about 400 mg., and preferably about 300 mg., based on the weight of the free base. A preferred route of administration for the netupitant is oral. In terms of binding to NK_1 receptors, the netupitant preferably binds to at least 80 or even 85% of NK_1 receptors in the striatum seventy-two hours after administration. As of ninety six hours after administration, the netupitant preferably binds less than 70, 60, 50 or even 40% of said NK_1 receptors.

The methods of the present invention are all effective at treating or preventing nausea and vomiting induced by numerous events, including chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), and post-operative nausea and vomiting ("PONV"). The method is preferably performed shortly before the emesis inducing event (i.e. no more than 1 or 2 hours before the event). The methods may be used to treat nausea and vomiting during the acute phase of emesis, or during the delayed phase.

The drugs specified by the individual embodiments may be administered by any suitable dosing regimen, as is well known in the art, but in a preferred embodiment the netupitant, 5-HT_3 antagonist and steroid are administered orally. A preferred oral dose of palonosetron ranges from about 0.075 to about 1.0 mg, or from about 0.25 to about 0.75 mg, but is preferably about 0.5 mg. A preferred oral dose of netupitant ranges from about 50 to 500 mg, or from about 200 to about 400 mg, but is preferably about 300 mg. A preferred dose of corticosteroid, preferably dexamethasone, is 12 mg administered orally or via injection on the first day of treatment, and 8 mg administered orally or via injection on the second, third and fourth days after said treatment.

It will be further understood that the netupitant can be administered in prodrug form, in which case the invention will provide a method of treatment by inducing plasma levels of netupitant, and in each case the plasma level of netupitant induced by the prodrug administration will correspond to the level attained by the administration of netupitant or its pharmaceutically acceptable salt, in the doses and routes of administration described herein.

Pharmaceutical Compositions

Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

Preferred modes of administrations of the active compounds are injectable and/or oral. These compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules (for oral use) or compressed into tablets (for oral or buccal use) or formulated into troches (for buccal use). For these purposes, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

Tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a gliding such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compounds can be administered as a component of an elixir, suspension, syrup, wafer, orally disintegrating film, orally disintegrating tablet, chewing gum or the like. A syrup

may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

Solutions or suspensions used for injection can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfate; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride, mannitol and dextrose. An injectable preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Combined Oral Dosage Forms

As discussed above, the invention provides versatile combined oral dosage forms of palonosetron and an NK1 antagonist that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation. In a preferred embodiment, the invention provides a capsule for oral administration made from a hard outer shell that houses one or more NK1 antagonist tablets and one or more palonosetron soft-gel capsules. The finished capsule and the tablet(s) and soft-gel capsule(s) housed within the capsule shell are all preferably formulated as immediate release dosage forms. Netupitant and casopitant, and their pharmaceutically acceptable salts, are particularly preferred NK_1 antagonists for the combined oral dosage forms of this invention.

While the NK1 antagonist is preferably formulated in a solid tablet, it will be understood that it can be formulated in any solid form that is suitable for oral administration including, for example, a tablet or capsule (hard or soft-gel). In a preferred embodiment, the NK1 antagonist is formulated in a tablet. The number of NK1 antagonist units contained within the combined dosage form can be, for example, from 1 to 10, 1 to 5, or 1 to 3. The netupitant units within the combined dosage form can provide anywhere from 50 to 500 mg of netupitant on an aggregate basis, preferably from 100 to 350 mg. Each netupitant unit preferably comprises from 50 to 200 mg of netupitant, more preferably 100 to 150 mg of netupitant, and most preferably 100 or 150 mg of netupitant.

The palonosetron can also be formulated in any solid form that is suitable for oral administration, although it is preferably formulated as a soft-gel capsule. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference. The number of palonosetron units within the combined dosage from can be, for example, from 1 to 5, from 1 to 3 or just 1. Each of the palonosetron units within the combined dosage form can provide anywhere from 0.01 to 5.0 mg palonosetron, preferably from 0.1 to 1.0 mg palonosetron on an aggregate basis. Each palonosetron unit will preferably comprise from 0.1 to 1.0 mg of palonosetron, most preferably about 0.25, 0.5, 0.75 or 1.0 mg of palonosetron.

FIG. **1** illustrates an exemplary embodiment of a combined oral dosage form of palonosetron and netupitant. The dosage form **10** comprises a two piece hard outer shell that includes a body **20** and a cap **22**. The dosage form **10** contains one palonosetron soft-gel capsule **30** (preferably containing 0.5 mg of palonosetron) and three netupitant tablets **40** (each preferably containing 100 mg of netupitant).

Hard Outer Shell

The hard outer shell of the present invention can be made of any pharmaceutically acceptable material that dissolves in gastric fluids. Preferred materials for the hard outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). In a particular embodiment of the invention, the hard outer shell has a maximum oxygen permeability. Preferably, the oxygen permeability is less about 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm).

The hard outer shell can be a continuous structure. Alternatively, the hard outer shell can be a two-piece hard capsule.

Soft-Gel Capsule

The soft-gel capsule used for the palonosetron preferably comprises a soft outer shell and a liquid inner fill composition comprising palonosetron hydrochloride. Non-limiting examples of suitable palonosetron soft-gel capsules are provided in PCT publication WO 2008/049552, the contents of which are hereby incorporated by reference.

The soft outer shell of the soft-gel capsule can contain any type of material that dissolves in gastric fluids. Preferred materials for the soft outer shell include, for example, gelatin, cellulose, starch, or hydroxypropyl methylcellulose (HPMC). The soft-gel capsule can further comprise shell excipients such as glycerin, sorbitol, and colorants/opacifers such as titanium dioxide. The soft-gel capsule can further include solvents such as purified water. In particular embodiments of the invention, the outer shell has a maximum oxygen permeability, preferably of no more than 1.0×10^{-3}, 5.0×10^{-4}, 1.0×10^{-4}, 5.0×10^{-5}, or even 2.0×10^{-5} ml·cm/(cm^2·24 hr. atm). Suitable soft-gel capsules include the 1.5-oval gelatine capsule shell manufactured by Catalent Pharma Solutions.

The liquid fill is preferably composed predominantly of one or more lipophilic components in an amount of from 50 wt. % to 99 wt. %, preferably from 75 wt. % to 98 wt. %. Preferred lipophilic components include, for example, mono- and di-glycerides of fatty acids, especially including the mono- and di-glycerides of capryl/capric acid. The liquid fill may also contain glycerin, preferably in an amount of from 1 to 15 wt. %, more preferably from 2 to 10 wt. %. In one preferred embodiment, both the shell and the inner fill composition comprise glycerin. In another preferred embodiment, the liquid fill comprises about 0.25, 0.50, 0.75 mg., or more of palonosetron as palonosetron hydrochloride.

The fill composition may comprise various means to facilitate the transition of palonosetron from the dosage form to the gastrointestinal fluids of the GI tract, so that the palonosetron may be more readily absorbed into the bloodstream. For example, the liquid fill composition may contain a surfactant, optimally in an amount of from 0.1 wt. % to 6 wt. %, from 0.5 wt. % to 5 wt. %, or from 1.0 wt. % to 3.0 wt. %. The liquid fill composition preferably comprises greater than 0.1, 0.5, or 1.0 wt. % of surfactant, and less than 10, 8, 5, 4, or even 4 wt. % of surfactant. A particularly preferred surfactant is polyglyceryl oleate.

Alternatively or in addition, the transitioning means for a liquid filled capsule may comprise water that forms a single phase or microemulsion with the other liquid ingredients in the excipient base. The liquid fill composition preferably comprises from 0.05 wt. % to 30 wt. % water, from 1 wt. % to 20 wt. % water, or from 2 wt. % to10 wt. % water. The liquid fill preferably comprises greater than 0.1, 0.5 or 1.0 wt. % water, and less than 20, 15, 10, 8 or 5 wt. % water.

The active agent, which is preferably palonosetron hydrochloride, is preferably present in the fill composition in an

amount ranging from 0.01 to 10.0 wt. %, from 0.05 to 5.0 wt. %, or from 0.1 wt. % to 2.0 wt. %. Alternatively, particularly stable formulations have been found where the concentration of palonosetron exceeds 0.3%, preferably at a concentration no greater than 1 wt. %.

Tablet

The tablets of the present invention can include from 20 to 95 wt. % of NK1 antagonist (preferably netupitant), and preferably comprises from 60 to 80 wt. % of netupitant. In addition, the tablets can contain diluents, disintegrants, surfactants, binders, glidants, and/or lubricants. In a particular embodiment, the tablet comprises from 5 to 25 wt. % of microcrystalline cellulose. The microcrystalline cellulose can function as a diluent and disintegrant, and preferably comprises 15 wt. % of the tablet. Another suitable disintegrant is sodium croscaramellose, which can be present in the tablet in an amount of from 1 to 5 wt. %, preferably 2 wt. %.

A suitable binder for use in the tablet is polyvinylpyrrolidone, which can be present in the tablet in an amount from 1 to 10 wt. % of the tablet, and preferably 5 wt. %. A suitable glidant for use in the tablet is colloidal silicon dioxide, which can be present in the tablet in an amount of 2 wt. %. Suitable lubricants for use in the tablet include sodium stearyl fumarate and magnesium stearate, which can be present in the tablet in an amount of 0.7 wt. % and 0.35 wt. %, respectively.

Application of the Combined Oral Dosage Forms

The invention further provides a method of treating emesis comprising orally administering to a patient suffering from emesis, or at risk for suffering emesis, a dosage form of the present invention. In still further embodiments, the invention provides methods of treating emesis by administering one or more of the dosage forms described herein. The dosage form is preferably administered shortly before the emesis inducing event (i.e. no more than 2 hours before the event). The emesis may be acute phase emesis (i.e. emesis experienced within about 24 hours of an emesis inducing event), or delayed emesis (i.e. emesis experienced after the acute phase, but within seven, six, five or four days of an emesis inducing event). The emesis may constitute chemotherapy induced nausea and vomiting ("CINV"), from moderately or highly emetogenic chemotherapy, radiation therapy induced nausea and vomiting ("RINV"), or postoperative nausea and vomiting ("PONV").

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.) but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at room temperature, and pressure is at or near atmospheric.

Example 1

Preparation of Oral Dosage Form

In a preferred embodiment the combination is administered in a capsule oral dosage form, wherein the capsule houses one or more soft-gel capsules for the palonosetron and one or more hard tablets for the netupitant. Table 1 below describes a representative formulation for a soft-gel capsule containing 0.5 mg of palonosetron, suitable for inclusion in such a hard outer shell.

TABLE 1

REPRESENTATIVE SOFT-GEL FORMULATION

Ingredient	Approximate Amount	Function
Fill Solution		
Palonosetron HC1	0.56[1]	Active
Mono- and di-glycerides of	62.19	Solvent vehicle
Glycerin, anhydrous, USP/Ph Eur	3.37	Plasticizer
Polyglyceryl oleate (Plurol Oleique CC 497)	0.87	Surfactant
Purified water, USP/Ph Eur	2.94	Co-solvent
Butylated hydroxyanisole (BHA), NF/Ph Eur	0.07	Antioxidant
Nitrogen	—	
Theoretical fill weight	70.00 mg	
Gelatine Capsule Shell, 1.5-oval (Catalent Pharma Solutions)[2]		
Gelatine (type 195), NF/Ph Eur	—	Shell
Sorbitol Special/Glycerin Blend 50/50	—	Plasticizer
Titanium dioxide, USP/Ph Eur	—	Colorant/ Opacifier
Purified water, USP/Ph Eur	—	Solvent

[1]Corresponds to 0.50 mg. free base

[2]Quantitative composition of capsule shell is proprietary to Catalent Pharma Solutions

Table 2 below describes a representative formulation for a tablet containing 100 mg. of netupitant, suitable for inclusion in a hard shell.

TABLE 2

REPRESENTATIVE TABLET FORMULATION

Ingredient	Approximate Amount (mg/Tablet)	Function
Netupitant, milled	100	Active
Microcrystalline cellulose pH 101	20.5	Diluent and disintegrant
Sucrose Lauric Acid Esters	10.0	Surfactant
Polyvinilpyrrolidone K30	7.0	Binder
Sodium croscaramellose	3.0	Disintegrant
Colloidal Silicon Dioxide	3.0	Glidant
Sodium Stearyl Fumarate	1.0	Lubricant
Magnesium Stearate	0.5	Lubricant
Total weight	145 mg	

Example 2

Pharmacokinetics of Combined Dosage Form

Objective

The effects of palonosetron on the pharmacokinetics (PK) of netupitant and the effects of netupitant on the PK of palonosetron were examined in healthy volunteers.

Methods

A randomized, open, 3-way crossover study was conducted. Each subject participated in 3 treatment periods, each lasting approximately 12 days (Day −1 to Day 11). The treatment periods were separated by wash-out periods of no less than 14 days (between Day 1 of any 2 consecutive treatment periods).

The following treatments were investigated:

Treatment A: oral netupitant 450 mg. administered as single dose of three 150 mg. capsules.

Treatment B: oral palonosetron 0.75 mg. and oral netupitant 450 mg. administered simultaneously as three capsules of 150 mg. netupitant followed by 1 capsule of 0.75 mg. palonosetron.

Treatment C: oral palonosetron 0.75 mg. administered as single dose as one 0.75 mg. capsule.

Doses were administered under fasting conditions. Subjects fasted over-night for approximately 10 hours. Water, however, was permitted up to 1 hour pre-dose. Food intake was permitted 4 hours post-dose, and water was allowed ad libitum 1 hour post-dose.

Doses were administered with the subject in an upright position. The subjects remained in an upright position for 4 hours post-dose. The capsules were swallowed whole with 250 mL of room-temperature tap water. Repeated PK blood sampling (for netupitant and/or palonosetron) was performed.

Results

The primary PK variables assessed for netupitant and palonosetron were the maximum plasma concentration observed (C_{max}), the area under the plasma concentration versus time curve from time zero to the last quantifiable sampling time point (t) (AUC_{0-t}), and the area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-inf}). The secondary PK variables assessed were the terminal elimination half-life ($t_{1/2,z}$), and the time at which the maximum plasma concentration was observed (t_{max}). Results are depicted in below Tables 3 and 4, as well as FIGS. **2** and **3**.

TABLE 3

Summary of Netupitant Pharmacokinetic Parameters

Parameter	Netupitant 450 mg	Palonosetron 0.75 mg + Netupitant 450 mg
AUC_{0-t} [h * µg/L]	22808 (7270)	22775 (10064)
AUC_{0-inf} [h * µg/L]	25927 (10156)	26241 (13219)
C_{max} [µg/L]	650.2 (257.8)	659.7 (325.7)
t_{max} (h)	4.50 (3.00; 24.00)	4.50 (3.00; 23.95)
$t_{1/2,z}$ (h)	71.81 (37.10; 261.61)	78.31 (50.17; 196.13)

Mean and SD are shown, except for t_{max} and $t_{1/2}$, where median and range are shown.

As can be seen in Table 4 below, palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron, for example, the greater AUC, the larger C_{max}, the shorter t_{max}, (the median t_{max} was 0.5 hour shorter after administration of palonosetron in combination with netupitant), and the longer $t_{1/2,z}$.

TABLE 4

Summary of Palonosetron Pharmacokinetic Parameters

Parameter	Palonosetron 0.75 mg	Palonosetron 0.75 mg +
AUC_{0-t} [h * µg/L]	67415 (19554)	74230 (24866)
AUC_{0-inf} [h * µg/L]	70813 (20415)	77254 (25402)
C_{max} [µg/L]	1638.4 (415.5)	1863.1 (487.1)
t_{max} (h)	5.02 (4.00; 8.00)	4.50 (3.00; 6.02)
$t_{1/2,z}$ (h)	34.73 (19.61; 70.46)	36.91 (20.23; 56.08)

Mean and SD are shown, except for t_{max} and $t_{1/2}$, where median and range are shown.

Example 3

Netupitant+Dexamethasone Drug Interaction Study

The effect of netupitant on orally administered dexamethasone pharmacokinetics was evaluated in this study. This was a randomized, open, 3-period crossover study utilizing an incomplete Latin Square design where subjects were given dexamethasone alone, or oral Netupitant 100 mg., 300 mg. or 450 mg. each given with dexamethasone. Netupitant was given orally on Day 1 only. The dexamethasone regimen for each treatment was 20 mg. orally Day 1, followed by 8 mg. orally every 12 hours from Day 2 through Day 4. Nineteen subjects (12 male and 7 female) completed the study (i.e., all 3 treatment periods).

Mean plasma concentrations of dexamethasone were higher when dexamethasone was co-administered with netupitant (FIG. **4**). The increase appeared to be dependant on the netupitant exposure.

The AUC_{0-24} (Day 1) of dexamethasone increased 1.5, 1.7 and 1.8-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. The AUC_{24-36} (Day 2) of dexamethasone increased 2.1, 2.4 and 2.6-fold and AUC_{84-108} and AUC_{84-inf} (Day 4) increased 1.7, 2.4 and 2.7-fold, with co-administration of 100, 300 and 450 mg. netupitant, respectively. Dexamethasone C_{max} on Day 1 was only slightly affected by co-administration of netupitant (1.1-fold increase during co-administration with 100 and 300 mg. netupitant, respectively, and 1.2-fold increase during co-administration with 450 mg. netupitant). C_{max} on Day 2 and Day 4 was increased approximately 1.7-fold in subjects administered netupitant. Dexamethasone C_{min} on Days 2-4 was increased approximately 2.8, 4.3 and 4.6-fold with co-administration of 100, 300 and 450 mg. netupitant, respectively. This clearly shows that the co-administration of netupitant and dexamethasone enhances the bioavailability of dexamethasone and provides a better therapeutic window of dexamethasone.

Example 4

Netupitant Pet Receptor Occupancy Study

This was a randomized, open-label, positron emission tomography (PET) study using 11C-GR205171 as tracer in 6 healthy male volunteers (2 per dose level) receiving single doses of netupitant (100, 300 or 450 mg) to investigate the degree of occupancy of NK_1 receptors in human brain, and to determine the relationship between plasma concentration of netupitant and NK_1 receptor occupancy (RO).

The anticipated high NK_1-RO (90% or higher) close to the expected C_{max} (6 hours post dose) was reached for striatum, occipital cortex, frontal cortex and anterior cingulate in 3 of 6 subjects of whom 1 received 300 mg. and 2 received 450 mg. of netupitant as a single oral dose.

All doses showed a relatively long duration of blockade of NK_1 receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK_1-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK_1-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK_1-RO_s with increasing netupitant dose. (FIG. **5**)

Example 5

Clinical Efficacy Study

A phase 2 trial evaluated three single doses of netupitant combined with palonosetron and dexamethasone compared to palonosetron alone and dexamethasone to obtain dose ranging information for netupitant used with oral palonosetron in the CINV patient population.

The objective of the study was to compare the efficacy and safety of three single oral doses of netupitant combined with oral palonosetron and given with dexamethasone, versus oral palonosetron-alone given with dexamethasone (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg. dose was used in each applicable treatment group in this study.

This was a multicenter, randomized, double-blind, double-dummy, parallel group, stratified study. Eligible patients were randomized (stratified by gender) to one of the following treatment groups:

Group 1—0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)

Group 2—100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

Group 3—200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 4—300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)

Group 5—125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

In addition, a Group 6 was added to the analysis for comparative purposes, based on the results reported by Grunberg et al., Support Cancer Care (2009) 17:589-594:

Group 6—285 mg. oral aprepitant plus 20 mg. oral dexamethasone plus 0.2 mg. palonosetron i.v. (all on Day 1) then 80 mg. oral aprepitant

The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication) within 120 hours after the start of the highly emetogenic chemotherapy administration. Secondary efficacy endpoints were:

Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);

Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS<5 mm); No significant nausea (maximumVAS<25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.

Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);

Severity of nausea for the overall, acute and delayed phase; • Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

Complete response rates are summarized in Table 5. The percent of patients with complete response over 0-120 hours after start of cisplatin administration was 76.5% in the palonosetron alone group and 87.4%, 87.6%, and 89.6% in the netupitant 100 mg., 200 mg., and 300 mg. groups, respectively. Differences from palonosetron-alone were greater than 10% (10.9% to 13.2%). All doses of netupitant were statistically superior to palonosetron alone (p-value=0.004 for the netupitant 300 mg. combination group).

TABLE 5

COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)
CR, Overall Phase, 0-120 h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, −24 h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120 h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

Table 6 summarizes results for main secondary endpoints. In the overall phase, 76.5% of patients in the palonosetron-alone group did not experience emesis, while 87.4, 87.6, and 91.1% of patients did not experience emesis in the netupitant 100 mg., 200 mg. and 300 mg. combination groups, respectively ($p<0.05$ for all doses).

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value, 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis
**As reported by Grunberg et al., Support Cancer Care (2009) 17:589-594

Example 7

Comparative Results of Aprepitant Dosing Regimen

The following Table 8 reports the results observed for an aprepitant dosing regimen, as described in the FDA approved prescribing information for aprepitant, which demonstrates, among other things, that aprepitant has no meaningful effect on nausea. Table 7 reports the dosing regimen:

TABLE 7

Treatment Regimen	Day 1	Day 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)

TABLE 8

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 - Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase[1]	89	78	<0.001
Delayed Phase[2]	75	56	<0.001

TABLE 8-continued

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 - Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
[1]Acute phase: 0 to 24 hours post-cisplatin treatment.
[2]Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

The invention claimed is:

1. A method of preventing acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

2. A method of achieving complete response during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

3. A method of preventing nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

4. The method of claim **1**, wherein said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy.

5. The method of claim **1**, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

6. The method of claim **1**, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.

7. The method of claim **1**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors seventy-two hours after said administration.

8. The method of claim **1**, wherein said method achieves complete response in said subject.

9. The method of claim **1**, wherein said method achieves no emesis in said subject.

10. The method of claim **1**, wherein said method achieves no rescue medication in said subject.

11. The method of claim **1**, wherein said method prevents nausea in said subject.

12. The method of claim **1**, wherein said blood levels of netupitant are independently effective to prevent acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy.

13. The method of claim **2**, wherein said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy.

14. The method of claim **2**, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

15. The method of claim **2**, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.

16. The method of claim **2**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors seventy-two hours after said administration.

17. The method of claim **2**, wherein said method prevents nausea in said subject.

18. The method of claim **2**, wherein said blood levels of netupitant are independently effective to produce complete response in a subject receiving highly emetogenic cancer chemotherapy.

19. The method of claim **3**, wherein said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy.

20. The method of claim **3**, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

21. The method of claim **3**, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.

22. The method of claim **3**, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors seventy-two hours after said administration.

23. The method of claim **3**, wherein said blood levels of netupitant are independently effective to prevent nausea in a subject receiving highly emetogenic cancer chemotherapy.

* * * * *

Exhibit J

US011312698B2

(12) **United States Patent**
Fadini et al.

(10) **Patent No.: US 11,312,698 B2**
(45) **Date of Patent: *Apr. 26, 2022**

(54) **FOSNETUPITANT CHLORIDE HYDROCHLORIDE HAVING IMPROVED STABILITY**

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(73) Assignee: **Helsinn Healthcare SA**, Lugano/Pazzallo (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/896,135**

(22) Filed: **Jun. 8, 2020**

(65) **Prior Publication Data**

US 2020/0399240 A1 Dec. 24, 2020

Related U.S. Application Data

(63) Continuation of application No. 16/228,835, filed on Dec. 21, 2018, now Pat. No. 10,717,721, which is a continuation of application No. 15/874,325, filed on Jan. 18, 2018, now Pat. No. 10,208,073, which is a continuation of application No. 15/194,984, filed on Jun. 28, 2016, now Pat. No. 9,908,907, which is a continuation of application No. 14/360,991, filed as application No. PCT/US2012/066778 on Nov. 28, 2012, now Pat. No. 9,403,772, which is a continuation-in-part of application No. 13/478,361, filed on May 23, 2012, now Pat. No. 8,426,450.

(60) Provisional application No. 61/564,537, filed on Nov. 29, 2011.

(51) **Int. Cl.**

A61K 31/4427	(2006.01)
A61K 31/496	(2006.01)
C07D 213/74	(2006.01)
C07D 401/04	(2006.01)
A61K 31/56	(2006.01)
A61K 45/06	(2006.01)
C07D 213/89	(2006.01)
A61K 31/44	(2006.01)
A61K 31/473	(2006.01)
A61K 31/675	(2006.01)
C07F 9/6509	(2006.01)
A61P 25/22	(2006.01)
A61P 13/10	(2006.01)
A61P 25/24	(2006.01)
A61P 1/08	(2006.01)
A61K 9/00	(2006.01)
A61K 31/573	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 401/04*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/473*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 31/573*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 45/06*** (2013.01); ***A61P 1/08*** (2018.01); ***A61P 13/10*** (2018.01); ***A61P 25/22*** (2018.01); ***A61P 25/24*** (2018.01); ***C07D 213/74*** (2013.01); ***C07D 213/89*** (2013.01); ***C07F 9/650952*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/4427; A61K 31/496; C07D 213/74; C07D 401/04

USPC 514/253.01, 352; 544/360; 546/304

See application file for complete search history.

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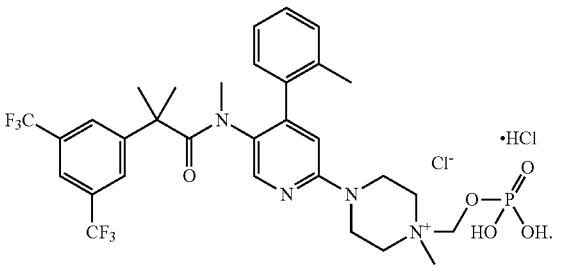
(Continued)

Primary Examiner — Douglas M Willis
(74) *Attorney, Agent, or Firm* — Clark G. Sullivan

(57) **ABSTRACT**

Fosnetupitant chloride hydrochloride having improved stability, characterized by the following chemical structure:



12 Claims, 1 Drawing Sheet

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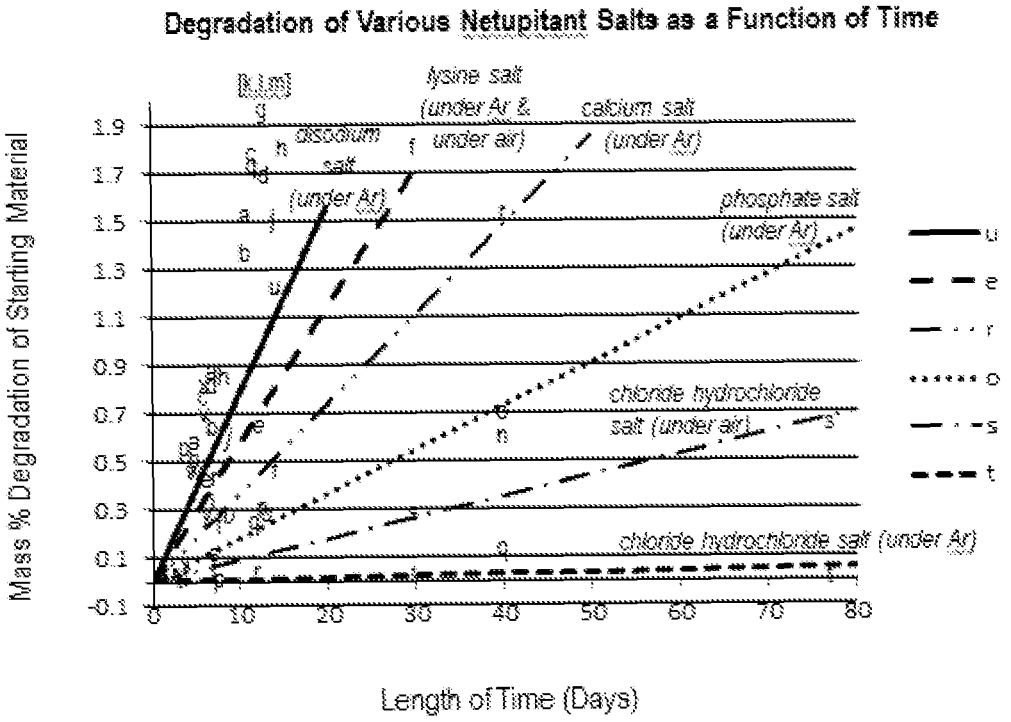


Degradation Behavior Over Time for Various Salts of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phos-phonooxy)methyl)piperazin-1-ium.

FOSNETUPITANT CHLORIDE HYDROCHLORIDE HAVING IMPROVED STABILITY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 61/564,537, filed Nov. 29, 2011, and is a continuation in part of U.S. Non-provisional application Ser. No. 13/478,361, filed May 23, 2012.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel 4-phenyl-pyridine compounds, and medical uses thereof, particularly in the prevention and/or treatment of medical conditions modulated by the neurokinin (NK_1) receptor.

Description of Related Art

Substance P is an 11-amino acid neuropeptide present reportedly involved in various pathological conditions including asthma, inflammation, pain, psoriasis, migraine, dyskinesia, cystitis, schizophrenia, emesis and anxiety, due to its localizations and functions. Substance P is an agonist for the NK1 receptor, and causes intracellular signal transduction through its interaction with the NK1 receptor.

The NK1 receptor has been reported to be implicated in various disorders and diseases, and various NK_1 antagonists have been developed for the purpose of treating or preventing such disorders and diseases. For example, Kramer et al. (*Science* 281 (5383), 1640-1645, 1988) reports clinical trials for NK_1 receptor antagonists in the treatment of anxiety, depression, psychosis, schizophrenia and emesis. Gesztesi et al. (*Anesthesiology* 93(4), 931-937, 2000) also reports the use of NK_1 receptor antagonists in the treatment of emesis

U.S. Pat. No. 6,297,375 to Hoffmann-La Roche describes a class of 4-phenyl-pyridine compounds that are NK_1 antagonists which are useful for treating CNS disorders, such as depression, anxiety or emesis. Netupitant is a selective NK_1 receptor antagonist among these 4-phenyl-pyridine compounds, and is currently under clinical development in combination with palonosetron (a $5\text{-}HT_3$ receptor antagonist) for the prevention of chemotherapy-induced-nausea and vomiting (CINV) by Helsinn Healthcare.

Mono-N-oxide derivatives of 4-phenyl-pyridine compounds are described in U.S. Pat. No. 6,747,026 to Hoffmann-La Roche. These N-oxide derivatives are reportedly intended to overcome limitations on the parent compounds that would otherwise limit their clinical usefulness, such as solubility or pharmacokinetic limitations. However, no physicochemical or biological data of the mono-N-oxide derivatives are reported in the '026 patent.

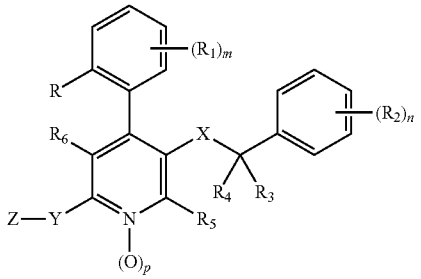
U.S. Pat. No. 5,985,856 to the University of Kansas describes water soluble N-phosphoryloxymethyl derivatives of secondary and tertiary amines, and the use of such derivatives to improve the solubility profiles of loxapine and cinnarizine. The '856 patent does not disclose how the N-phosphoryloxymethyl moiety would affect other critical attributes of the drug product, such as prodrug structure(s), prodrug stability, synthetic cost, and selectivity of the phosphoryloxymethylation protocol.

In view of the above, there is a need to find new derivatives of and methods for making 4-phenyl-pyridine compounds that are effective NK_1 receptor antagonists, and that have enhanced physicochemical and/or biological properties.

SUMMARY

In view of the foregoing, the inventors have developed a novel class of 4-phenyl-pyridine derivatives that are particularly well-suited for antagonizing the NK_1 receptor and that have the following general formula (I):

Formula (I)



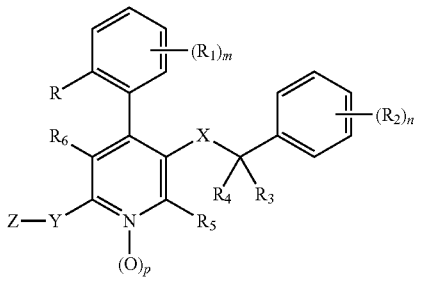
and pharmaceutically acceptable salts or adducts thereof.

Compounds of formula (I), also known as 4-phenyl-pyridine derivatives, are particularly useful for preventing and/or treating diseases that are pathophysiologically related to the NK_1 receptor in a subject. Accordingly, in another embodiment the invention provides a method of treating a disease that is mediated by the NK_1 receptor, comprising administering to said subject a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof.

Also disclosed are pharmaceutical compositions for preventing and/or treating diseases which are pathophysiologically related to NK_1 receptor in a subject, comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

In one embodiment the invention is a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof,

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocy-

cloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

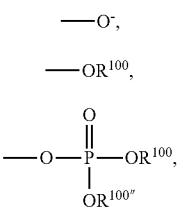
R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkyl$NR^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —$C(O)NR^{101}R^{102}$, -alkylO, -alky$NR^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:

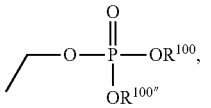


(Ia)

(Ib)

(Ic)

-continued



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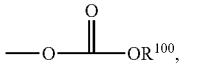
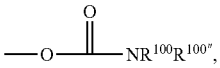
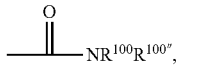


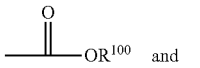
(Ie)



(If)

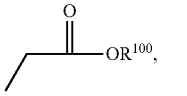


(Ig)



(Ih)

and



(Ii)

where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, 4 or 5;

p is 0 or 1; and

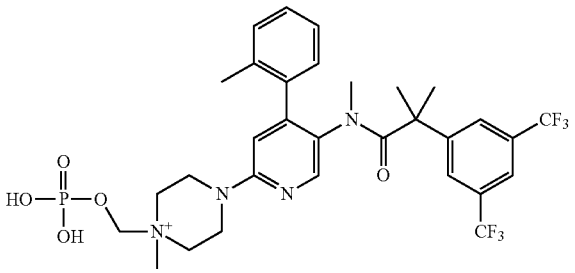
with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one.

In another embodiment the invention is the use of a therapeutically effective amount of a compound of formula (I) as defined above or a pharmaceutically acceptable salt or adduct thereof, in the manufacture of a medicament which is able to treat emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof.

In an alternative embodiment the invention is a method of treating emesis, bladder dysfunction, depression or anxiety, in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) as defined above.

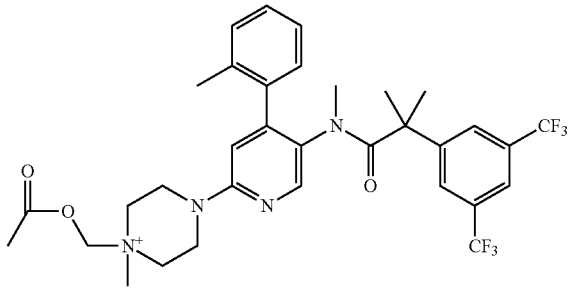
In still another embodiment the invention is a compound selected from the group consisting of:

GA1



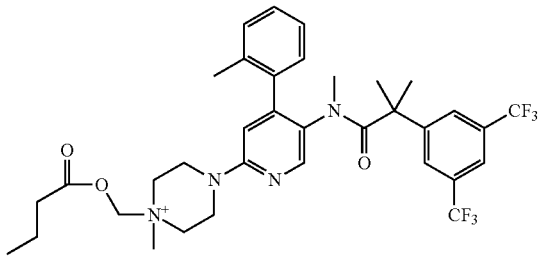
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,

GA2



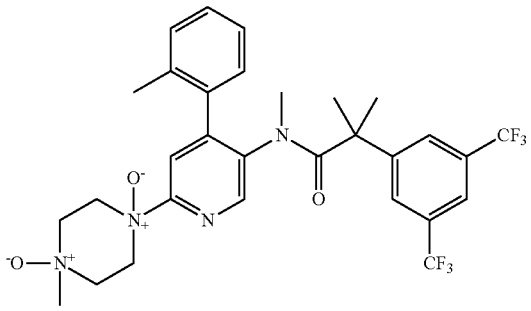
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,

GA3



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,

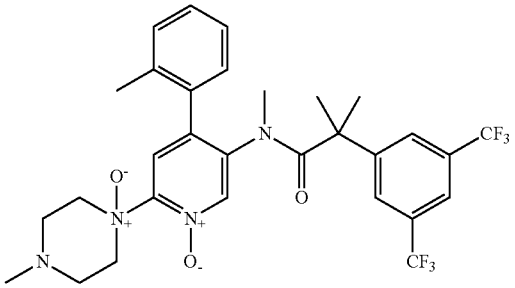
GA4



1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

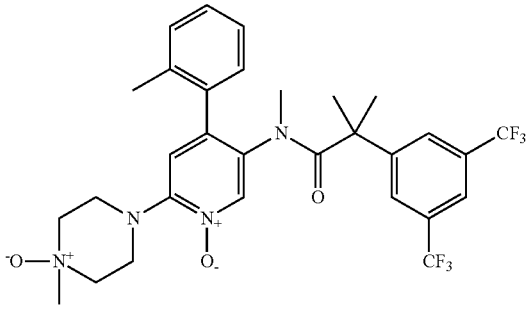
-continued

GA5



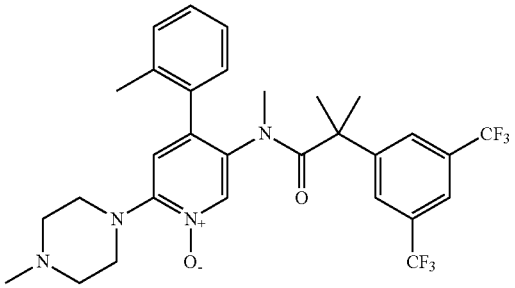
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

GA6



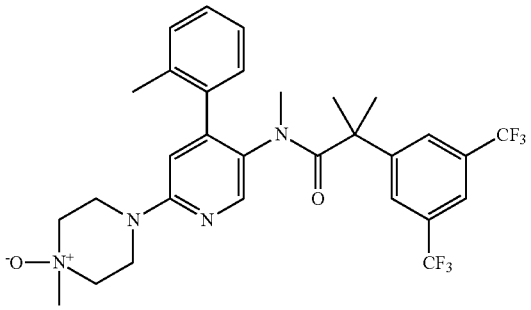
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine-1-oxide,

GA7



5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and

GA8

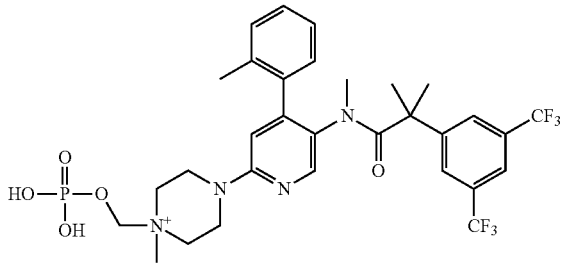


4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

or a pharmaceutically acceptable salt or adduct thereof.

In a further embodiment the invention is a compound of formula GA1,

formula GA1



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium

or a pharmaceutically acceptable salt or adduct thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** reproduces stability data for various salts of 4-(5-(2-(3,5-bis(trifluoro-methyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphornooxy)methyl)piperazin-1-ium.

DETAILED DESCRIPTION

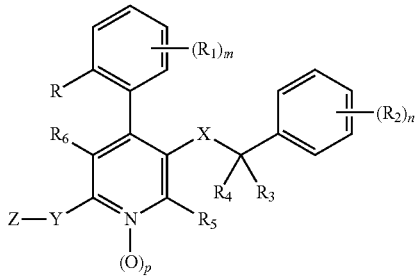
Before the present compounds, compositions, articles, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods or specific treatment methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

Materials

A. Compounds

Disclosed are compounds and pharmaceutically acceptable salts or adducts thereof represented by formula (I):

Formula (I)



wherein:

R is selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkylN$R^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkylN$R^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_1 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R_2 together with the atoms and/or other substituent(s) on the same phenyl ring form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

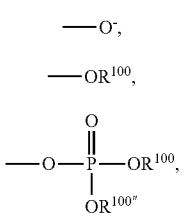
R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkylN$R^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_3 and R_4, together with the atoms connecting the same form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, —OR^{101}, —$NR^{101}R^{102}$, —$NR^{101}C(O)R^{102}$, —$C(O)R^{101}$, —$C(O)OR^{101}$, —$C(O)NR^{101}R^{102}$, -alkylN$R^{101}R^{102}$, —$S(O)_2R^{102}$, —SR^{101}, —$S(O)_2NR^{101}R^{102}$, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

X is selected from the group consisting of —C(O)$NR^{101}R^{102}$, -alkylO, -alkyN$R^{101}R^{102}$, —$NR^{101}C(O)$ and —NR^{101}alkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Y is selected from the group consisting of —$NR^{101}R^{102}$, —NR^{101}alkylOH, —$NR^{101}S(O)_2$alkyl, —$NR^{101}S(O)_2$phenyl, —N═CH—$NR^{101}R^{102}$, heterocycloalkyl and heterocycloalkylalkyl, each optionally independently substituted with one or more independent R^{103} substituents;

Z is a structural formula selected from the group consisting of:



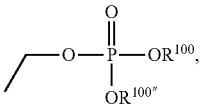
(Ia)

(Ib)

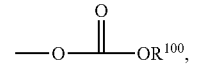
(Ic)

-continued

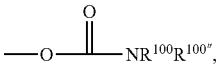
(Id)



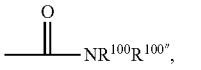
(Ie)



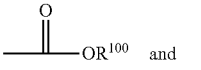
(If)



(Ig)

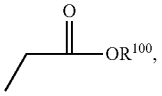


(Ih)



and

(Ii)



where formula (Ia) refers to an oxide;

R^{100}, $R^{100''}$, R^{101}, R^{102} and R^{103} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, —OR^{104}, oxide, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, heteroarylalkyl, —$C(O)R^{104}$, —$C(O)OR^{104}$, —$C(O)NR^{104}R^{105}$, —$NR^{104}R^{105}$, —$NR^{104}S(O)_2R^{105}$, —$NR^{104}C(O)R^{105}$, —$S(O)_2R^{104}$, —SR^{104} and —$S(O)_2NR^{104}R^{105}$, each optionally independently substituted with one or more independent R^{103} substituents; or R^{101}, R^{102}, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents; or R^{100}, $R^{100''}$, together with the atoms connecting the same, form a fused or non-fused mono, bicyclic or tricyclic heterocyclic or carbocyclic ring which is optionally independently substituted with one or more R^{103} substituents;

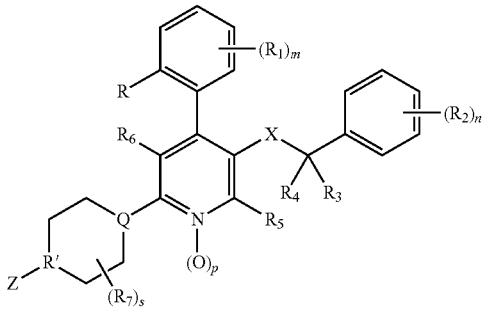
R^{104} and R^{105} are each independently selected from the group consisting of hydrogen, cyano, —NO_2, hydroxy, oxide, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl, halogen, alkoxy, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl and heteroarylalkyl;

m is from 0 to 4; n is from 0 to 5; p is from 0 to 1; and with a proviso that if a non-pyridine N-Oxide ($N^-\rightarrow O^+$) is present on the compound of Formula (I), then the total number of N-Oxide on the compound of Formula (I) is more than one. In another embodiment, the invention excludes all N-oxide forms.

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein R, R_1, R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, hydroxy, amino, alkyl, alkenyl, cycloalkyl, halogen, cyano, —OR^{101} and CF_3.

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein X is —$NR^{101}C(O)$. In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein Y is a heterocycloalkyl or heterocycloalkylalkyl. In some still other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (II):

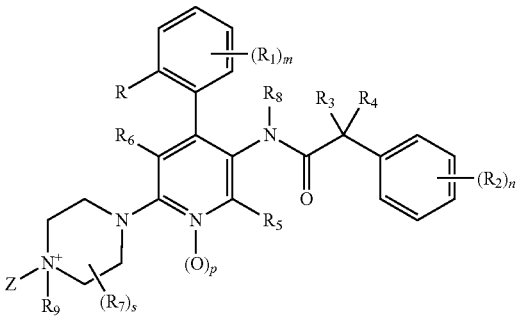
Formula (II)



where Q and R' are each independently selected from the group consisting of C, O, S, and N, each optionally independently substituted with one or more independent R^{103} substituents; R_7 is selected from the group selected from hydrogen, alkoxy, alkoxyalkyl, —OR^{101}, hydroxy, hydroxyalkyl, amino, alkyl, alkenyl, cycloalkyl and halogen, each optionally independently substituted with one or more independent R^{103} substituents; s is from 0 to 4; and all other variables are defined as for formula (I).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (III):

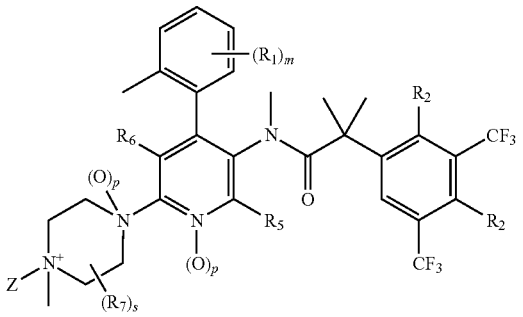
Formula (III)



where R_8 is selected from the group consisting of hydrogen, alkyl, alkenyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; R_9 is alkyl or cycloalkyl, each optionally substituted with one or more independent R^{103} substituents; and all other radicals are defined as for formula (I) and formula (II).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (IV):

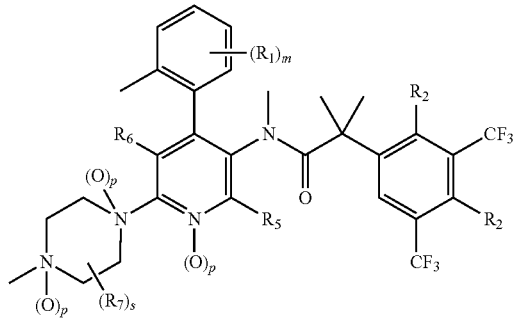
Formula (IV)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II) and formula (III).

In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (V):

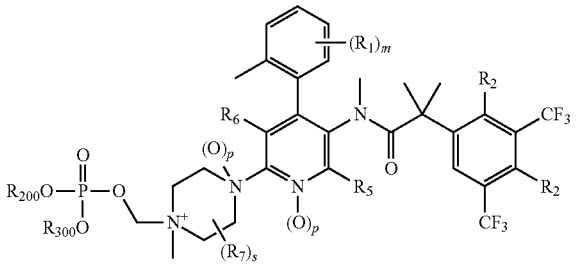
Formula (V)



where p is independently 0 or 1; and all other radicals are defined as for formula (I), formula (II), formula (III) and formula (IV).

In some other forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) has a structure of formula (VI):

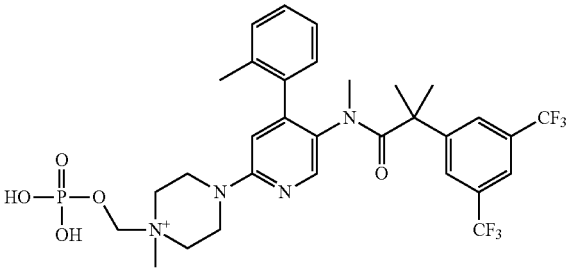
Formula (VI)



where R_{200} and R_{300} are each independently selected from the group consisting of hydrogen, alkyl and cycloalkyl, each optionally independently substituted with one or more independent R^{103} substituents; or R_{200} and R_{300} are each independently an organic or inorganic cation; p is independently 0 or 1; and all other radicals are defined according to formula (I), formula (II), formula (III), formula (IV) and formula (V).

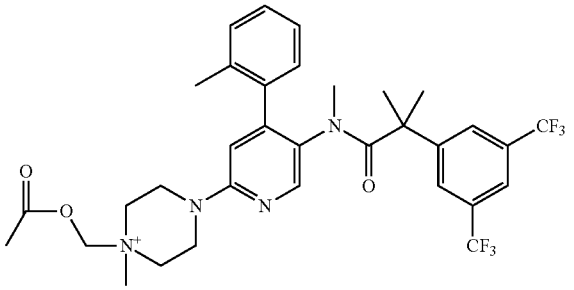
In some forms, the compounds as presently disclosed are compounds of formula (I), or pharmaceutically acceptable salts or adducts thereof, wherein the compound of formula (I) is a compound selected from the group consisting of.

GA1



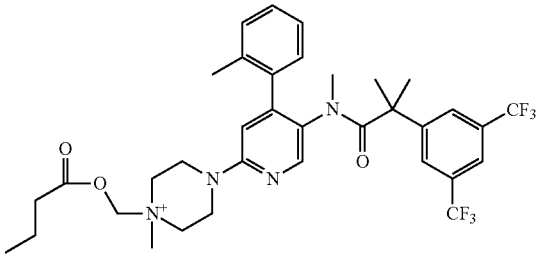
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium,

GA2



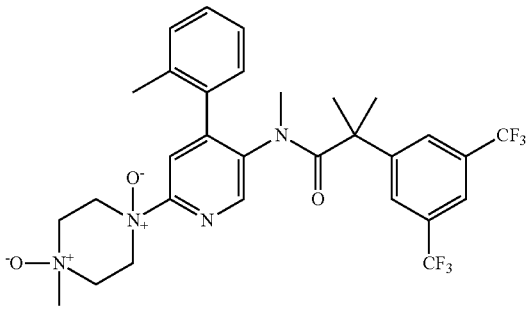
1-(acetoxymethyl)-4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazin-1-ium,

GA3



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-((butyryloxy)methyl)-1-methylpiperazin-1-ium,

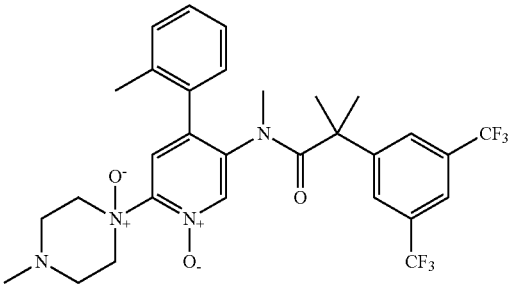
GA4



1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide,

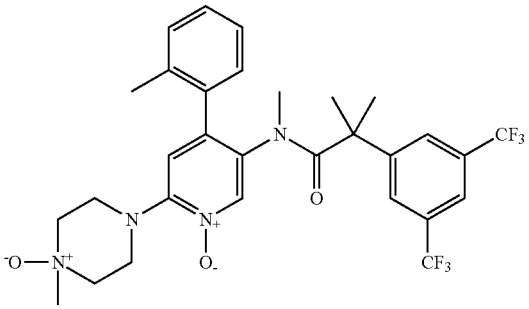
-continued

GA5



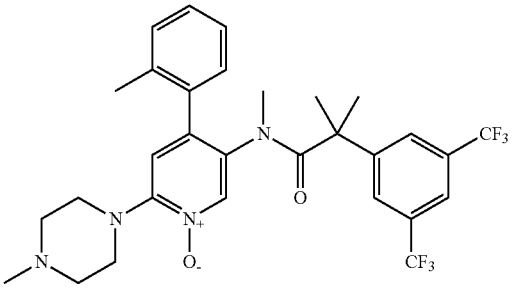
1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1-oxide,

GA6



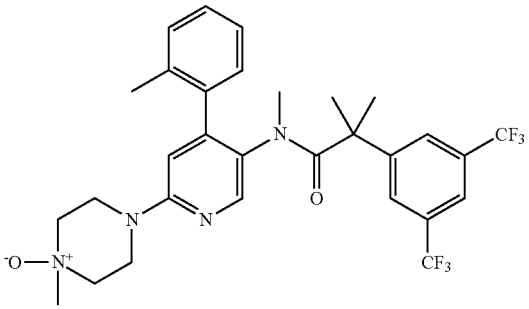
4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl) pyridin-2-yl)-1-methylpiperazine-1-oxide,

GA7



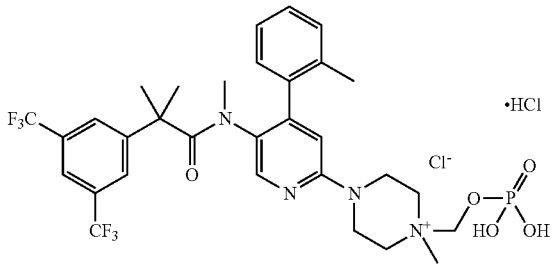
5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide, and

GA8



4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide.

A particular preferred compound is the chloride hydrochloride HCl salt of GA1 having the following chemical structure which, it has been found, is tremendously resistant to decoupling of the oxo-phosphonomethyl, and reversion of the active moiety to its parent state.



Salts and Adducts

The disclosed compositions and compounds can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound can be advantageous due to one or more of the salt's physical properties, such as enhanced storage stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound, such as the disclosed compounds, with an acid whose anion, or a base whose cation is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the salts of the disclosed compounds are non-toxic "pharmaceutically acceptable salts." Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the disclosed compounds which are generally prepared by reacting the free base with a suitable organic or inorganic acid.

Suitable pharmaceutically acceptable acid addition salts of the disclosed compounds, when possible include those derived from inorganic acids, such as hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, metaphosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclylic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, cam-

phorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

Furthermore, where the disclosed compounds carry an acidic moiety, suitable pharmaceutically acceptable salts thereof can include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., copper, calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In some forms, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts can be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be quaternized with agents such as lower alkyl (C1-C6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibuytl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others. In some forms, hemisalts of acids and bases can also be formed, for example, hemisulphate and hemicalcium salts. The disclosed compounds can exist in both unsolvated and solvated forms. A "solvate" as used herein is a nonaqueous solution or dispersion in which there is a noncovalent or easily dispersible combination between solvent and solute, or dispersion means and disperse phase.

The disclosed compositions and compounds can be used in the form of adducts derived by formation of Lewis pairs, covalently linked adducts e.g. between N atoms and carbonyl-containing reactants, hydrates and alcoholates, host-guest adducts containing molecular species not bonded or associated with the medicinal compound, and other clathrates.

Depending on the particular compound, an adduct of the compound can be advantageous due to one or more of the adduct's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, an adduct of a compound also can be used as an aid in the isolation, purification, and/or resolution of the compound.

Where an adduct is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the adduct preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable adduct" refers to an adduct prepared by combining a compound, such as the disclosed compounds, with a gas, water, solvent, Lewis base, carbonyl-containing molecule, or guest molecule that is generally considered suitable for human consumption. Pharmaceutically acceptable addition species are particularly useful as products of the disclosed methods because of their greater aqueous solubility relative to the parent compound. For use in medicine, the adducts of the disclosed compounds are non-toxic "pharmaceutically acceptable adducts." Adducts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic adducts of the disclosed compounds which are generally prepared by reacting a compound of the invention with a suitable organic or inorganic addition species.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, include those derived from Lewis bases such as boric acid, aluminum hydroxide, organic sulfoxides, organic sulfones, organic sulfonium salts, H_3PO_3, siloxanes, and other Lewis bases.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from covalent bonding between an oxygen, nitrogen or sulfur atom of the compound and carbon dioxide, low alkyl aldehyde or ketone, vanillin, amino acid, or a nucleic acid.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from inclusion of an unbonded gas such as dioxygen, dinitrogen, carbon dioxide, nitrous oxide, ethyl ether, or other gas, contained within but not bonded to a crystalline or amorphous phase of the compound.

Suitable pharmaceutically acceptable adducts of the disclosed compounds, when possible, also include those derived from association of a molecule of the compound with water, a pharmaceutically acceptable lower alkyl alcohol, or another pharmaceutically acceptable solvent that is associated in a molecular ratio with the compound.

In one embodiment the adduct is optionally a clathrate.

General Synthetic Schemes

The compounds of the formula (I) (and other disclosed compounds), or their pharmaceutically acceptable salts or adducts, can be prepared by the methods as illustrated by examples described in the "Examples" section, together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. The starting materials used herein are commercially available or can be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the Compendium of Organic Synthesis Methods, Vol. I-VI (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below. During any of the following synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1991, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, and P. G. M. Wuts and T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 2006. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

The invention further provides methods for making suitable prodrugs of the 4-phenyl-pyridine derivatives. In one embodiment the invention provides a one-step, acid-free synthesis for functionalizing tertiary amines by reaction with chloromethyl dialkyl phosphate esters to create (phosphooxy)methyl prodrugs that are substrates for phosphatase enzymes. By contrast the prior art had required multiple synthetic steps for comparable reactions, including requiring the use of proton scavengers during initial reaction and requiring strong acid to deprotect the phosphate group in another step. In another embodiment the invention provides methods for making chloromethyl dialkyl phosphate esters having suitable purity and economy, because the quality of phosphate ester compositions from commercial sources is too low to provide acceptable yields for reactions according to the invention. In an additional embodiment the invention provides a method to stabilize the (phosphooxy)methyl prodrugs according to the invention by combination with

two equivalents of hydrochloric acid, because whereas the prior art preferred the use of dibasic salts of (phosphooxy) methyl substituents for quaternary ammonium salts in prodrugs, the present invention had found that such salts are unstable and reform the underlying drug during storage.

Definition of Terms

The term "alkyl" refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen) containing from one to twenty carbon atoms; in one embodiment from one to twelve carbon atoms; in another embodiment, from one to ten carbon atoms; in another embodiment, from one to six carbon atoms; and in another embodiment, from one to four carbon atoms. Examples of such substituents include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" refers to a linear or branched-chain hydrocarbyl substituent containing one or more double bonds and from two to twenty carbon atoms; in another embodiment, from two to twelve carbon atoms; in another embodiment, from two to six carbon atoms; and in another embodiment, from two to four carbon atoms. Examples of alkenyl include ethenyl (also known as vinyl), allyl, propenyl (including 1-propenyl and 2-propenyl) and butenyl (including 1-butenyl, 2-butenyl and 3-butenyl). The term "alkenyl" embraces substituents having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "benzyl" refers to methyl radical substituted with phenyl.

The term "carbocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring). A carbocyclic ring typically contains from 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A "carbocyclic ring system" alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenyl, and decalinyl.

The term "heterocyclic ring" refers to a saturated cyclic, partially saturated cyclic, or aromatic ring containing from 3 to 14 ring atoms ("ring atoms" are the atoms bound together to form the ring), in which at least one of the ring atoms is a heteroatom that is oxygen, nitrogen, or sulfur, with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

The term "cycloalkyl" refers to a saturated carbocyclic substituent having three to fourteen carbon atoms. In one embodiment, a cycloalkyl substituent has three to ten carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the cycloalkyl group. When such a fused cycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a carbon atom of the cycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "cycloalkenyl" refers to a partially unsaturated carbocyclic substituent having three to fourteen carbon atoms, typically three to ten carbon atoms. Examples of cycloalkenyl include cyclobutenyl, cyclopentenyl, and cyclohexenyl.

A cycloalkyl or cycloalkenyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. Alternatively, 2 or 3 rings may be fused together, such as bicyclodecanyl and decalinyl.

The term "aryl" refers to an aromatic substituent containing one ring or two or three fused rings. The aryl substituent may have six to eighteen carbon atoms. As an example, the aryl substituent may have six to fourteen carbon atoms. The term "aryl" may refer to substituents such as phenyl, naphthyl and anthracenyl. The term "aryl" also includes substituents such as phenyl, naphthyl and anthracenyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such a fused aryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O. Examples of aryl groups include accordingly phenyl, naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, anthracenyl, phenanthrenyl, benzonaphthenyl (also known as "phenalenyl"), and fluorenyl.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (e.g., alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, etc.) is indicated by the prefix "C_x-C_y-," wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl refers to saturated cycloalkyl containing from 3 to 6 carbon ring atoms.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (e.g., heteroaryl or heterocycloalkyl) is indicated by the prefix "X-Y-membered", wherein x is the minimum and y is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, 5-8-membered heterocycloalkyl refers to a heterocycloalkyl containing from 5 to 8 atoms, including one or more heteroatoms, in the cyclic moiety of the heterocycloalkyl.

The term "hydrogen" refers to hydrogen substituent, and may be depicted as —H.

The term "hydroxy" refers to —OH. When used in combination with another term(s), the prefix "hydroxy" indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol.

The term "hydroxyalkyl" refers to an alkyl that is substituted with at least one hydroxy substituent. Examples of hydroxyalkyl include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl.

The term "nitro" means —NO_2.

The term "cyano" (also referred to as "nitrile") —CN.

The term "carbonyl" means —C(O)—.

The term "amino" refers to —NH_2.

The term "alkylamino" refers to an amino group, wherein at least one alkyl chain is bonded to the amino nitrogen in place of a hydrogen atom. Examples of alkylamino substituents include monoalkylamino such as methylamino (exemplified by the formula —NH(CH_3)), and dialkylamino such as dimethylamino.

The term "aminocarbonyl" means —C(O)—NH_2.

The term "halogen" refers to fluorine (which may be depicted as —F), chlorine (which may be depicted as —Cl), bromine (which may be depicted as —Br), or iodine (which may be depicted as —I). In one embodiment, the halogen is chlorine. In another embodiment, the halogen is a fluorine.

The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen substituents. For example, haloalkyl refers to an alkyl that is substituted with at least one halogen substituent. The term "oxo" refers to =O.

The term "oxy" refers to an ether substituent, and may be depicted as —O—.

The term "alkoxy" refers to an alkyl linked to an oxygen, which may also be represented as —O—R, wherein the R represents the alkyl group. Examples of alkoxy include methoxy, ethoxy, propoxy and butoxy.

The term "alkylthio" means —S-alkyl. For example, "methylthio" is —S—CH_3. Other examples of alkylthio include ethylthio, propylthio, butylthio, and hexylthio.

The term "alkylcarbonyl" means —C(O)-alkyl. Examples of alkylcarbonyl include methylcarbonyl, propylcarbonyl, butylcarbonyl, pentylcabonyl, and hexylcarbonyl.

The term "aminoalkylcarbonyl" means —C(O)-alkyl-NH_2.

The term "alkoxycarbonyl" means —C(O)—O-alkyl. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, and hexyloxycarbonyl. In another embodiment, where the carbon atom of the carbonyl is attached to a carbon atom of a second alkyl, the resulting functional group is an ester.

The terms "thio" and "thia" mean a divalent sulfur atom and such a substituent may be depicted as —S—. For example, a thioether is represented as "alkyl-thio-alkyl" or, alternatively, alkyl-S-alkyl.

The term "thiol" refers to a sulfhydryl substituent, and may be depicted as —SH.

The term "thione" refers to =S.

The term "sulfonyl" refers to —$S(O)_2$—. Thus, for example, "alkyl-sulfonyl-alkyl" refers to alkyl-$S(O)_2$-alkyl. Examples of alkylsulfonyl include methylsulfonyl, ethylsulfonyl, and propylsulfonyl.

The term "aminosulfonyl" means —$S(O)_2$—NH_2.

The term "sulfinyl" or "sulfoxido" means —S(O)—. Thus, for example, "alkylsulfinylalkyl" or "alkylsulfoxidoalkyl" refers to alkyl-S(O)-alkyl. Exemplary alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, butylsulfinyl, and hexylsulfinyl.

The term "heterocycloalkyl" refers to a saturated or partially saturated ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heterocycloalkyl alternatively may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (e.g., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

Examples of heterocycloalkyl include, but not limited to, azacyclobutane, 1,3-diazatidine, pyrrolidine, 2-pyrroline, 3-pyrroline, 2-imidazoline, imidazolidine, 2-pyrazoline, pyrazolidine, piperidine, 1,2-diazacyclohexane, 1,3-diazacyclohexane, 1,4-diazacyclohexane, octahydroazocine, oxacyclobutane, tetrahydrofuran, tetrahydropyran, 1,2-dioxacyclohexane, 1,3-dioxacyclohexane, 1,4-dioxacyclohexane, 1,3-dioxolane, thiacyclobutane, thiocyclopentane, 1,3-dithiolane, thiacyclohexane, 1,4-dithiane, 1,3-oxathialane, morpholine, 1,4-thiaxane, 1,3,5-trithiane and thiomorpholine.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocyclocalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or to a 5-10-membered heteroaromatic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "heteroaryl" refers to an aromatic ring structure containing from 5 to 14 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings.

Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl. The term "heteroaryl" also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring.

Examples of single-ring heteroaryls include furanyl, dihydrofuranyl, tetradydrofuranyl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiaediazolyl, oxathiazolyl, oxadiazolyl (including oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (in-

cluding 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl" or "pyrimidyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

Examples of 2-fused-ring heteroaryls include, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

Examples of 3-fused-ring heteroaryls or heterocycloalkyls include 5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline, 4,5-dihydroimidazo[4,5,1-hi]indole, 4,5,6,7-tetrahydroimidazo[4,5,1-jk][1]benzazepine, and dibenzofuranyl.

The term "heteroaryl" also includes substituents such as pyridyl and quinolinyl that are fused to a C_4-C_{10} carbocyclic ring, such as a C_5 or a C_6 carbocyclic ring, or to a 4-10-membered heterocyclic ring, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. The fused C_4-C_{10} carbocyclic or 4-10-membered heterocyclic ring may be optionally substituted with halogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, or =O.

The term "ethylene" refers to the group —CH_2—CH_2—. The term "ethynelene" refers to the group —CH=CH—. The term "propylene" refers to the group —CH_2—CH_2—CH_2—. The term "butylene" refers to the group —CH_2—CH_2—CH_2—CH_2—. The term "methylenoxy" refers to the group —CH_2—O—. The term "methylenethioxy" refers to the group —CH_2—S—. The term "methylenamino" refers to the group —CH_2—N(H)—. The term "ethylenoxy" refers to the group —CH_2—CH_2—O—. The term "ethylenethioxy" refers to the group —CH_2—CH_2—S—. The term "ethylenamino" refers to the group —CH_2—CH_2—N(H)—.

A substituent is "substitutable" if it comprises at least one carbon, sulfur, oxygen or nitrogen atom that is bonded to one or more hydrogen atoms. Thus, for example, hydrogen, halogen, and cyano do not fall within this definition. If a substituent is described as being "substituted," a non-hydrogen substituent is in the place of a hydrogen substituent on a carbon, oxygen, sulfur or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen substituent is in the place of a hydrogen substituent on the alkyl substituent.

If a substituent is described as being "optionally substituted," the substituent may be either (1) not substituted, or (2) substituted. When a substituent is comprised of multiple moieties, unless otherwise indicated, it is the intention for the final moiety to serve as the point of attachment to the remainder of the molecule. For example, in a substituent A-B-C, moiety C is attached to the remainder of the molecule. If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

Pharmaceutical Compositions

Pharmaceutical compositions for preventing and/or treating a subject are further provided comprising a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or adduct thereof, and one or more pharmaceutically acceptable excipients.

A "pharmaceutically acceptable" excipient is one that is not biologically or otherwise undesirable, i.e., the material can be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The carrier can be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. The carrier can be a solid, a liquid, or both.

The disclosed compounds can be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment or prevention intended. The active compounds and compositions, for example, can be administered orally, rectally, parenterally, ocularly, inhalationaly, or topically. In particular, administration can be epicutaneous, inhalational, enema, conjunctival, eye drops, ear drops, alveolar, nasal, intranasal, vaginal, intravaginal, transvaginal, ocular, intraocular, transocular, enteral, oral, intraoral, transoral, intestinal, rectal, intrarectal, transrectal, injection, infusion, intravenous, intraarterial, intramuscular, intracerebral, intraventricular, intracerebroventricular, intracardiac, subcutaneous, intraosseous, intradermal, intrathecal, intraperitoneal, intravesical, intracavernosal, intramedullar, intraocular, intracranial, transdermal, transmucosal, transnasal, inhalational, intracisternal, epidural, peridural, intravitreal, etc.

Suitable carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A. R. Gennaro, Mack Publishing Company, Easton, Pa., 1995. Oral administration of a solid dose form can be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one of the disclosed compound or compositions. In some forms, the oral administration can be in a powder or granule form. In some forms, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of formula I are ordinarily combined with one or more adjuvants. Such capsules or tablets can contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents or can be prepared with enteric coatings.

In some forms, oral administration can be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such com-

positions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In some forms, the disclosed compositions can comprise a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Typically, an appropriate amount of a pharmaceutically acceptable carrier is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically acceptable carrier include, but are not limited to, saline, Ringer's solution and dextrose solution. Other acceptable excipients include, but are not limited to, thickeners, diluents, buffers, preservatives, surface active agents and the like.

Other carrier materials and modes of administration known in the pharmaceutical art can also be used. The disclosed pharmaceutical compositions can be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3^{rd} Ed.), American Pharmaceutical Association, Washington, 1999.

The disclosed compounds can be used, alone or in combination with other therapeutic agents, in the treatment or prevention of various conditions or disease states. The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds can be administered simultaneously, concurrently or sequentially.

Disclosed are pharmaceutical compositions comprising an effective amount of a compound of the invention or a pharmaceutically accepted salt, solvate, clathrate, or prodrug thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions may further comprise additional agents. These compositions are useful for modulating the activity of the neurokinin (NK_1) receptor, thus to improve the prevention and treatment of NK_1 receptor associated diseases such as nausea and vomiting, bladder dysfunction, depression or anxiety.

In some forms, disclosed are pharmaceutical compositions for preventing and/or treating a subject comprising a therapeutically effective amount of a compound according to formula (I), and one or more pharmaceutically acceptable excipients. In some other forms, disclosed are pharmaceutical compositions, further comprising one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof.

Methods

All of the methods of the invention may be practiced with a compound of the invention alone, or in combination with other agents.

Treating

The above-described compounds and compositions are useful for the inhibition, reduction, prevention, and/or treatment of diseases which are pathophysiologically modulated by the neurokinin (NK_1) receptor. Accordingly, in some forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, comprising administering to a subject a therapeutically effective amount of a compound of formula (I) as disclosed above, or a pharmaceutically acceptable salt or adduct thereof.

Suitable subjects can include mammalian subjects. Mammals include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In some forms, humans are the subjects. Human subjects can be of either gender and at any stage of development.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said disease is nausea and vomiting, bladder dysfunction, depression or anxiety.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting (CINV), radiation therapy induced nausea and vomiting (RINV), or post-operative nausea and vomiting (PONV).

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said nausea and vomiting is an acute and/or delayed phases of CINV.

Acute emesis refers to the first twenty-four hour period following an emesis-inducing event. Delayed emesis refers to the second, third, fourth and fifth twenty-four hour periods following an emesis-inducing event. When a treatment is said to be effective during the delayed phase, it will be understood to mean that the effectiveness of the treatment is statistically significant during the entire delayed phase, regardless of whether the treatment is effective during any particular twenty-four hour period of the delayed phase. It will also be understood that the method can be defined based upon its effectiveness during any one of the twenty-four hour periods of the delayed phase. Thus, unless otherwise specified, any of the methods of treating nausea and/or vomiting during the delayed phases, as described herein, could also be practiced to treat nausea and/or vomiting during the second, third, fourth or fifth twenty-four hour periods following an emesis inducing event, or an combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said acute and/or delayed phases of CINV is induced by moderately or highly emetogenic chemotherapy. "Highly emetogenic chemotherapy" refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, cisplatin, cyclophosphamide ≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin. "Moderately emetogenic chemotherapy" refers to chemotherapy having a moderate degree of emetogenic potential, and includes chemotherapy based on carboplatin, cyclophosphamide <1500 mg/m^2, cytarabine >1 mg/m^2,

daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin.

In a preferred embodiment, the methods of the present invention are effective to treat acute and delayed emesis resulting from moderately and highly emetogenic chemotherapy, from a single dose of the netupitant derivative administered prior to chemotherapy, optionally in combination with other active ingredients.

A particularly preferred regimen for treating emesis, especially emesis induced by chemotherapy, involves a netupitant derivative of the present invention, a 5-HT3 antagonist such as palonosetron or a pharmaceutically acceptable salt thereof, and a corticosteroid such as dexamethasone. A suitable fixed regimen for treating acute and delayed CINV includes a single administration of the netupitant derivative on day one (preferably before chemotherapy), a single administration of the 5-HT3 antagonist on day 1 (preferably before chemotherapy). A corticosteroid is optionally added to the combination on day one and, when highly emetogenic chemotherapy is administered, on days 2, 3 and 4 as well. A preferred intravenous dose of palonosetron HCl is 0.25 mg based on the weight of the free base. Preferred dexamethasone doses are 12 mg. orally on day 1, followed by 8 mg. orally on days 2, 3 and 4 for highly emetogenic chemotherapy.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said bladder dysfunction is selected from urgency, frequency, pollakiuria, nocturia, low deferment time, suboptimal volume threshold, and neurogenic bladder, or a combination thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered by one or more routes selected from the group consisting of rectal, buccal, sublingual, intravenous, subcutaneous, intradermal, transdermal, intraperitoneal, oral, eye drops, parenteral and topical administration.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said administration is accomplished by intravenously administering a liquid form of said compound or a pharmaceutically acceptable salt or adduct thereof.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said administration is accomplished by orally administering said compound or a pharmaceutically acceptable salt or adduct thereof. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said netupitant derivative is orally administered at a dosage of from about 50 mg to about 500 mg, from about 100 mg to about 400 mg, from about 150 mg to about 350 mg, or about 300 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof is intravenously administered at a dosage of from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 75 mg to about 125 mg, or about 100 mg, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, particularly by derivatives of netupitant, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is formulated to have a concentration of from about 1 to about 20 mg/ml, from about 5 to about 15 mg/ml, from about 7 to about 2 mg/ml, or about 10 mg/ml, based on the weight of the netupitant component of the molecule.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said compound or a pharmaceutically acceptable salt or adduct thereof, is administered in a single dosage per day, a single dosage during a multi-day course of therapy (e.g., a five-day therapeutic regimen for delayed emesis), or in multiple dosages per day. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein said multiple dosages are from 2 to 4 dosages per day.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof. In some other forms, said therapeutic agent is a 5-HT_3 antagonist, a NK_1 antagonist or dexamethasone. In some other forms, said 5-HT_3 antagonist is ondansetron, palonosetron, granisetron or tropisetron, or a pharmaceutically acceptable salt thereof. In some still other forms, said 5-HT_3 antagonist is palonosetron or a pharmaceutically acceptable salt thereof. In some other forms, the oral dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.1 mg to about 2.0 mg, from about 0.25 mg to about 1.0 mg, from about 0.5 mg to about 0.75 mg, or about 0.5 mg. In some other forms, the intravenous dosage of palonosetron or a pharmaceutically acceptable salt thereof is from about 0.05 mg to about 2.0 mg, from about 0.075 mg to about 1.5 mg, from about 0.1 mg to about 1.0 mg, from about 0.25 mg to about 0.75 mg, or about 0.25 mg. In some other forms, said palonosetron or a pharmaceutically acceptable salt thereof is formulated to have a concentration of about 0.25 mg/5 mL.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, further comprising administering one or more therapeutic agents or a pharmaceutically acceptable salt thereof, wherein said therapeutic agent is a NK_1 antagonist which is 2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (netupitant). In one embodiment, the netupitant is administered in combination with GA8, and the ratio of GA8 to netupitant is greater than 1:200 or 1:100.

In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically

modulated by the NK_1 receptor, wherein the subject is a human. In some other forms, disclosed are methods of preventing and/or treating diseases which are pathophysiologically modulated by the NK_1 receptor, wherein the subject has been identified as needing treatment for the disease or the administration.

One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of a compound of Formula I for a given disease. In some other forms, disclosed are methods of preventing and/or treating a subject, further comprising one or more therapeutic agents.

More Definitions of Terms

1. A, an, the

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes not only single carriers but also mixtures of two or more such carriers, and the like.

2. Abbreviations

Abbreviations, which are well known to one of ordinary skill in the art, may be used (e.g., "h" or "hr" for hour or hours, "g" or "gm" for gram(s), "mL" for milliliters, and "rt" for room temperature, "nm" for nanometers, "M" for molar, and like abbreviations).

3. About

The term "about," when used to modify the quantity of an ingredient in a composition, concentrations, volumes, process temperature, process time, yields, flow rates, pressures, and like values, and ranges thereof, employed in describing the embodiments of the disclosure, refers to variation in the numerical quantity that can occur, for example, through typical measuring and handling procedures used for making compounds, compositions, concentrates or use formulations; through inadvertent error in these procedures; through differences in the manufacture, source, or purity of starting materials or ingredients used to carry out the methods; and like considerations. The term "about" also encompasses amounts that differ due to aging of a composition or formulation with a particular initial concentration or mixture, and amounts that differ due to mixing or processing a composition or formulation with a particular initial concentration or mixture. Whether modified by the term "about" the claims appended hereto include equivalents to these quantities.

4. Comprise

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps.

5. Publications

Throughout this application, various publications are referenced. In order to more fully document the state of the art to which this invention pertains, the disclosures of these publications are to be considered as being referenced individually, specifically and in their entireties for the material contained in them that is discussed in the sentence in which the reference is relied upon.

6. Subject

As used throughout, by a "subject" is meant an individual. Thus, the "subject" can include, for example, domesticated animals, such as cats, dogs, etc., livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.) mammals, non-human mammals, primates, non-human primates, rodents, birds, reptiles, amphibians, fish, and any other animal. The subject can be a mammal such as a primate or a human. The subject can also be a non-human.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary and are not intended to limit the disclosure. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

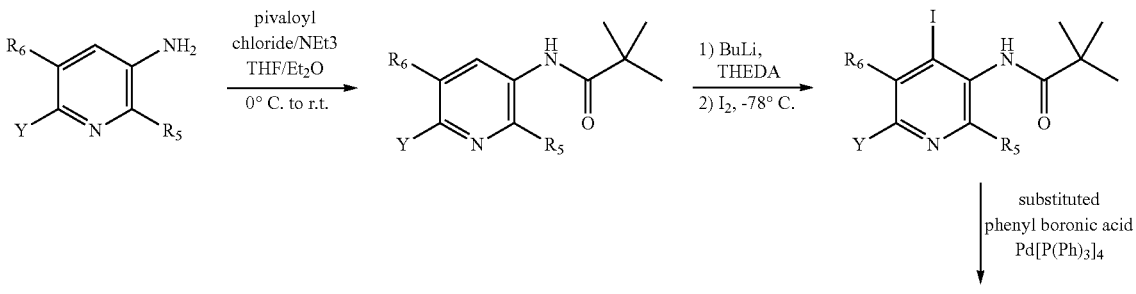
Example 1

Preparation of Compounds of Formula (I)

The following are examples of preparation of compounds of formula (I). This example is intended to be purely exemplary and is not intended to limit the disclosure.

General Scheme of Preparing Compounds of Formula (I)

Scheme 1



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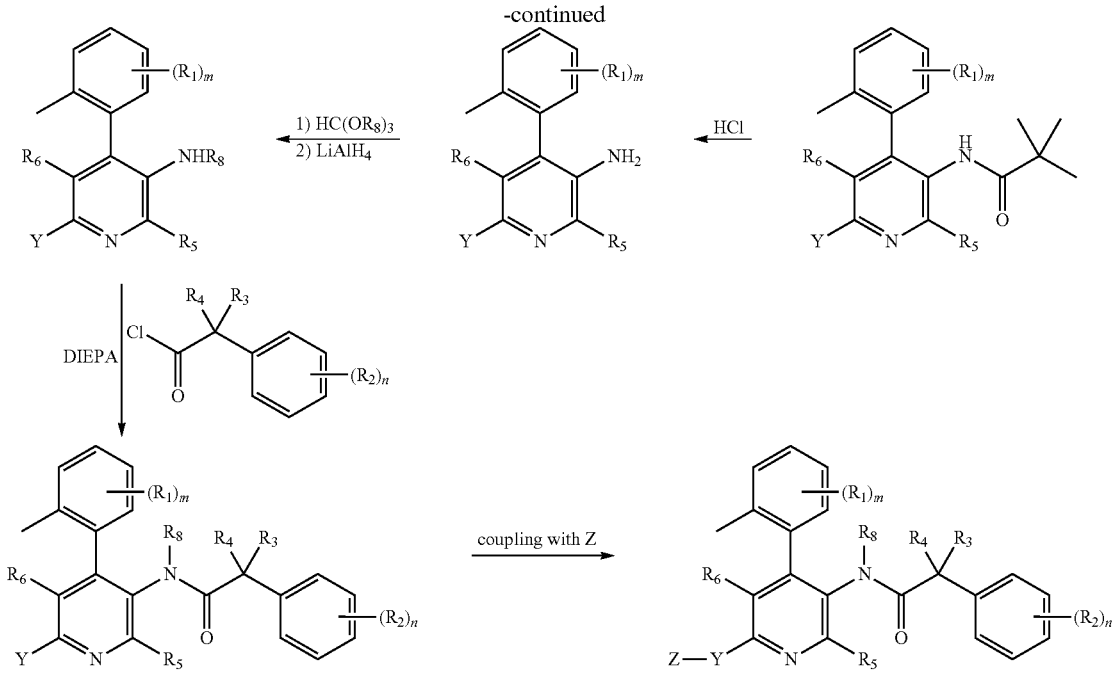
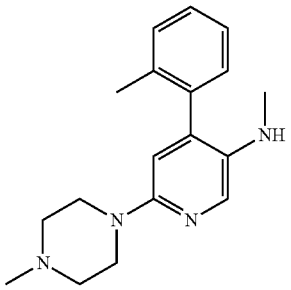


Other general procedures of preparing similar compounds to intermediate 1 of Scheme 1 are also disclosed in U.S. Pat. Nos. 6,303,790, 6,531,597, 6,297,375 and 6,479,483, which are referenced individually, specifically and in their entireties for the material contained in them that is relevant to the preparation of intermediate I.

Synthesis of methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine



Step 1:

13.0 g (82.5 mMol) 6-Chloro-nicotinic acid in 65 ml THE were cooled to 0° C. and 206.3 ml (206.3 mMol) o-tolyl-magnesium chloride solution (1M in TIF) were added over 45 minutes. The solution obtained was further stirred 3 hours at 0° C. and overnight at room temperature. It was cooled to −60° C. and 103.8 ml (1.8 Mol) acetic acid were added, followed by 35 ml THF and 44.24 g (165 mMol) manganese (III) acetate dihydrate. After 30 minutes at −60° C. and one hour at room temperature, the reaction mixture was filtered and THE removed under reduced pressure. The residue was partitioned between water and dichloromethane and extracted. The crude product was filtered on silica gel (eluent: ethyl acetate/toluene/formic acid 20:75:5) then partitioned between 200 ml aqueous half-saturated sodium carbonate solution and 100 ml dichloromethane. The organic phase was washed with 50 ml aqueous half-saturated sodium carbonate solution. The combined aqueous phases were acidified with 25 ml aqueous HCl 25% and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield 10.4 g (51%) of 6-chloro-4-o-tolyl-nicotinic acid as a yellow foam. MS (ISN): 246 (M−H, 100), 202 (M-CO_2H, 85), 166 (36).

Step 2:

To a solution of 8.0 g (32.3 mMol) 6-chloro-4-o-tolyl-nicotinic acid in 48.0 ml THE were added 3.1 ml (42.0 mMol) thionylchloride and 143 .mu.l (1.8 mMol) DMF. After 2 hours at 50° C., the reaction mixture was cooled to room temperature and added to a solution of 72.5 ml aqueous ammonium hydroxide 25% and 96 ml water cooled to 0° C. After 30 minutes at 0° C., THE was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate. Removal of the solvent yielded 7.8 g (98%) 6-chloro-4-o-tolyl-nicotinamide as a beige crystalline foam. MS (ISP): 247 ($M+H^+$, 100).

Step 3:

1.0 g (4.05 mMol) 6-Chloro-4-o-tolyl-nicotinamide in 9.0 ml 1-methyl-piperazine was heated to 100° C. for 2 hours. The excess N-methyl-piperazine was removed under high vacuum and the residue was filtered on silica gel (eluent: dichloromethane) to yield 1.2 g (95%) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide as a light yellow crystalline foam. MS (ISP): 311 ($M+H^+$, 100), 254 (62).

Step 4:

A solution of 0.2 g (0.6 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 1.0 ml methanol was added to a solution of 103 mg (2.6 mMol) sodium hydroxide in 1.47 ml (3.2 mMol) NaOCl (13%) and heated for 2 hours at 70° C. After removal of methanol, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and the residue filtered on silica gel (eluent: dichloromethane/methanol 4:1) to yield 100 mg (70%) 6-(4-methyl-

piperazin-1-yl)-4-o-tolyl-pyridin-3-ylamine as a brown resin. MS (ISP): 283 ($M+H^+$, 100), 226 (42).

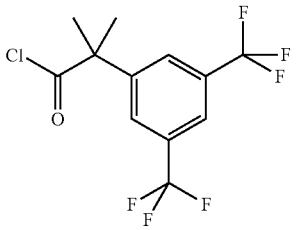
Step 5:

2.15 ml (11.6 mMol) Sodium methoxide in methanol were added over 30 minutes to a suspension of 0.85 g (4.6 mMol) N-bromosuccinimide in 5.0 ml dichloromethane cooled to −5° C. The reaction mixture was stirred 16 hours at −5° C. Still at this temperature, a solution of 1.0 g (3.1 mMol) 6-(4-methyl-piperazin-1-yl)-4-o-tolyl-nicotinamide in 5.0 ml methanol was added over 20 minutes and stirred for 5 hours. 7.1 ml (7.1 mMol) Aqueous HCl 1N and 20 ml dichloromethane were added. The phases were separated and the organic phase was washed with deionized water. The aqueous phases were extracted with dichloromethane, brought to pH=8 with aqueous NaOH 1N and further extracted with dichloromethane. The latter organic extracts were combined, dried (Na_2SO_4) and concentrated to yield 1.08 g (quant.) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester as a grey foam. MS (ISP): 341 ($M+H^+$, 100), 284 (35).

Step 6:

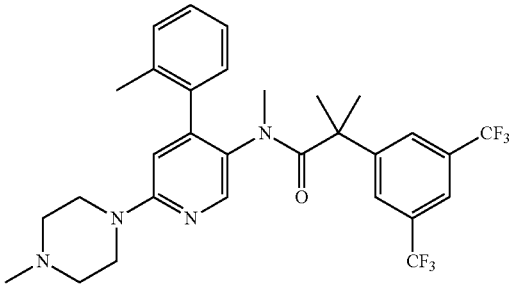
A solution of 0.5 g (1.4 mMol) [6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-carbamic acid methyl ester in 3.0 ml dichloromethane was added over 10 minutes to a solution of 1.98 ml (6.9 mMol) Red-A1.RTM. (70% in toluene) and 2.5 ml toluene (exothermic, cool with a water bath to avoid temperature to go >50° C.). The reaction mixture was stirred 2 hours at 50° C. in CH_2Cl_2, extracted with ethyl acetate and cooled to 0° C. 4 ml Aqueous NaOH 1N were carefully (exothermic) added over 15 minutes, followed by 20 ml ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with deionized water and brine, dried (Na_2SO_4) and concentrated under reduced pressure to yield 0.37 g (89%) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine as an orange resin. MS (ISP): 297 ($M+H^+$, 100).

Synthesis of 2-(3,5-bis-Trifluoromethyl-phenyl)-2-methyl-propionyl Chloride



15.0 g (50 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid were dissolved in 127.5 ml dichloromethane in the presence of 0.75 ml DMF. 8.76 ml (2 eq.) Oxalyl chloride were added and after 4.5 hours, the solution was rotary evaporated to dryness. 9 ml Toluene were added and the resulting solution was again rotary evaporated, then dried under high vacuum yielding 16.25 g (quant.) of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride as a yellow oil of 86% purity according to HPLC analysis. NMR (250 MHz, $CDCl_3$): 7.86 (br s, 1H); 7.77, (br s, 2H, $3H_{arom}$); 1.77 (s, 6H, 2 CH_3).

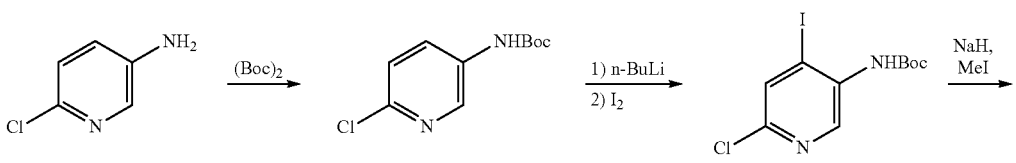
Synthesis of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl) pyridin-3-yl)propanamide (Netupitant)



A solution of 20 g (67.5 mmol) methyl-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-amine and 17.5 ml (101 mmol) N-ethyldiisopropylamine in 200 ml dichloromethane was cooled in an ice bath and a solution of 24 g (75 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride in 50 ml dichloromethane was added dropwise. The reaction mixture was warmed to 35-40° C. for 3 h, cooled to room temperature again and was stirred with 250 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 31.6 g (81%) of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide as white crystals. M.P. 155-157° C.; MS m/e (%): 579 ($M+H^+$, 100).

Synthesis of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide

Scheme 2



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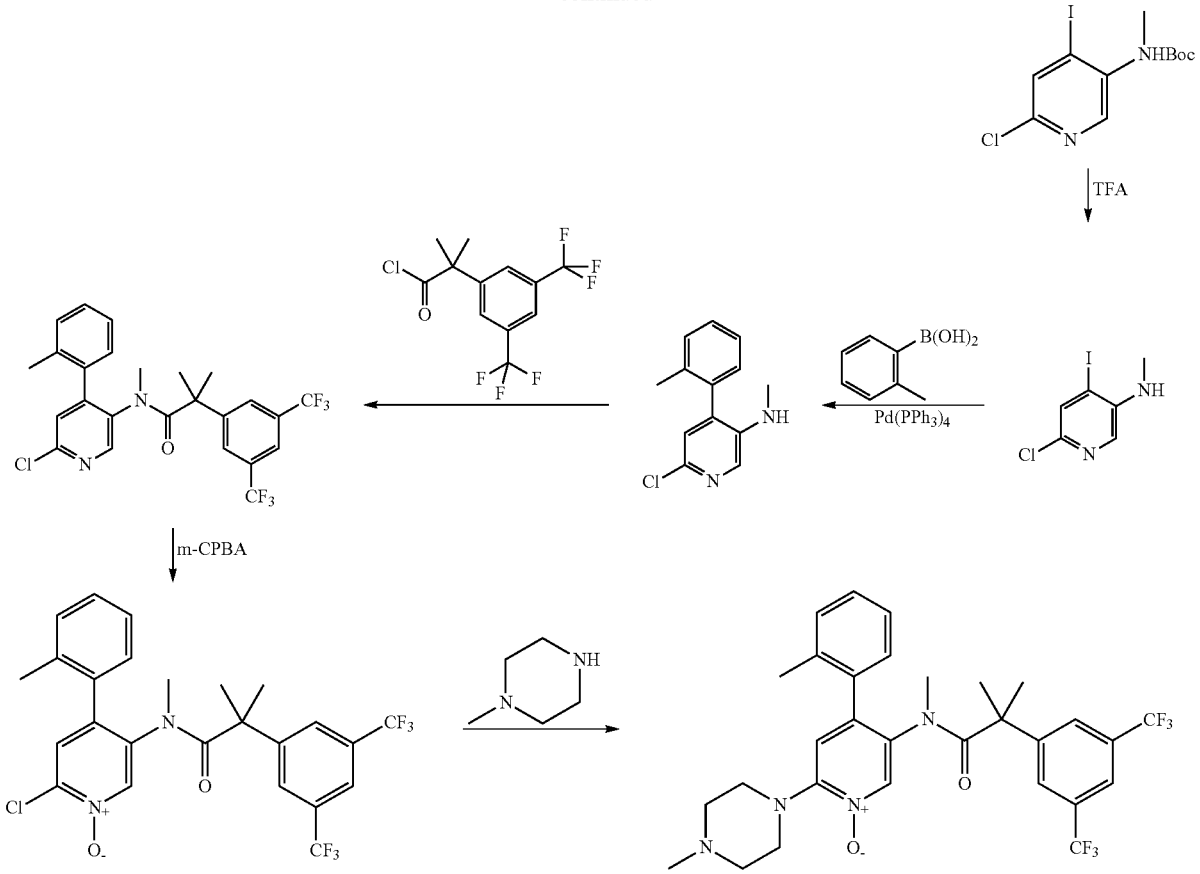


Step 1:

The solution of 6-chloropyridin-3-amine (115 g, 0.898 mol) and $(Boc)_2O$ (215.4 g, 0.988 mol) in 900 mL of dioxane was refluxed overnight. The resulting solution was poured into 1500 mL of water. The resulting solid was collected, washed with water and re-crystallized from EtOAc to afford 160 g tert-butyl (6-chloropyridin-3-yl) carbamate as a white solid (Yield: 78.2%).

Step 2:

To the solution of tert-butyl (6-chloropyridin-3-yl)carbamate (160 g, 0.7 mol) in 1 L of anhydrous THE was added n-BuLi (600 mL, 1.5 mol) at −78° C. under N_2 atmosphere. After the addition was finished, the solution was stirred at −78° C. for 30 min, and the solution of I_2 (177.68 g, 0.7 mol) in 800 mL of anhydrous THE was added. Then the solution was stirred at −78° C. for 4 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 80 g of tert-butyl (6-chloro-4-iodopyridin-3-yl)carbamate as a yellow solid (32.3%).

Step 3:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) carbamate (61 g, 0.172 mol) in 300 mL of anhydrous THE was added 60% NaH (7.6 g, 0.189 mol) at 0° C. under N_2 atmosphere. After the addition was finished, the solution was stirred for 30 min, and then the solution of MeI (26.92 g, 0.189 mol) in 100 mL of dry THE was added. Then the solution was stirred at 0° C. for 3 hrs. TLC indicated the reaction was over. Water was added for quench, and EtOAc was added to extract twice. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 63 g of crude tert-butyl (6-chloro-4-iodopyridin-3-yl)(methyl)carbamate used into the following de-protection without the further purification.

Step 4:

To the solution of tert-butyl (6-chloro-4-iodopyridin-3-yl) (methyl)carbamate (62.5 g, 0.172 mol) in 500 mL of anhydrous DCM was added 180 mL of TFA. Then the solution was stirred at room temperature for 4 hrs. Concentrated to remove the solvent, and purified by flash chromatography to afford 45.1 g 6-chloro-4-iodo-N-methylpyridin-3-amine as a yellow solid (Yield: 97.3%).

Step 5:

To the solution of 6-chloro-4-iodo-N-methylpyridin-3-amine (40.3 g, 0.15 mol) and 2-methylbenzene boric acid (24.5 g, 0.18 mol) in 600 mL of anhydrous toluene was added 400 mL of 2 N aq. Na_2CO_3 solution, $Pd(OAc)_2$ (3.36 g, 15 mmol) and PPh_3 (7.87 g, 0.03 mmol). The solution was stirred at 100° C. for 2 hrs. Cooled to room temperature, and diluted with water. EtOAc was added to extract twice. The combined organic phases were washed with water and brine consecutively, dried over Na_2SO_4, concentrated and purified by flash chromatography to afford 19 g 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine as a white solid (Yield: 54.6%).

Step 6:

To the solution of 6-chloro-N-methyl-4-(o-tolyl)pyridin-3-amine (18.87 g, 81.3 mmol) and DMAP (29.8 g, 243.9 mmol) in 200 mL of anhydrous toluene was added the

solution of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride (28.5 g, 89.4 mmol) in toluene under N_2 atmosphere. The solution was heated at 120° C. for 23 hrs. Cooled to room temperature, poured into 1 L of 5% aq. $NaHCO_3$ solution, and extracted with EtOAc twice. The combined organic phases were washed by water and brine consecutively, dried over Na_2SO_4, filtered and purified by flash chromatography to afford 35 g 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide as a white solid (Yield: 83.9%).

Step 7:

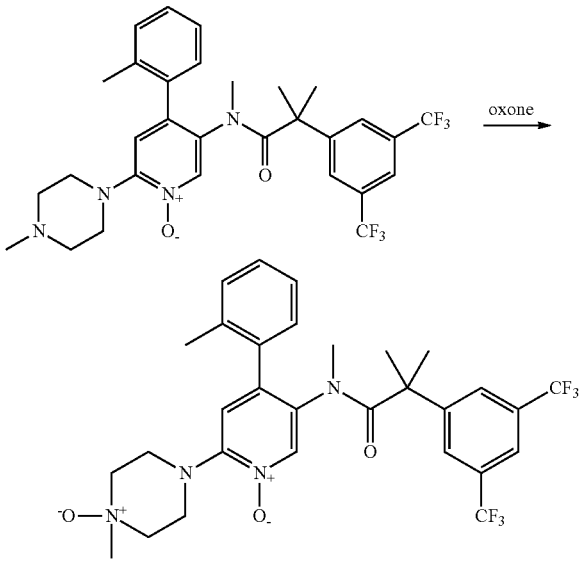
To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N-(6-chloro-4-(o-tolyl)pyridin-3-yl)-N,2-dimethylpropanamide (5.14 g, 10 mmol) in 60 mL of DCM was added m-CPBA (6.92 g, 40 mmol) at 0° C. under N_2 atmosphere. Then the solution was stirred overnight at room temperature. 1 N aq. NaOH solution was added to wash twice for removing the excess m-CPBA and a side product. The organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated to afford 5.11 g of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 96.4%).

Step 8:

To the solution of crude 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-chloro-4-(o-tolyl)pyridine 1-oxide (5.1 g, 9.62 mmol) in 80 mL of n-BuOH was added N-methylpiperazine (7.41 g, 74.1 mmol) under N_2 atmosphere. Then the solution was stirred at 80° C. overnight. Concentrated and purified by flash chromatography to afford 4.98 g 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide as a white solid (Yield: 87.2%). ^{1}HNMR (CDCl3, 400 MHz) δ 8.15 (s, 1H), 7.93 (s, 1H), 7.78 (s, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.17 (m, 1H), 7.07 (s, 1H), 5.50 (s, 3H), 2.72 (d, J=4.4 Hz, 4H), 2.57 (m, 3H), 2.40 (s, 3H), 2.23 (s, 3H), 1.45~1.20 (m, 6H).

Synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide

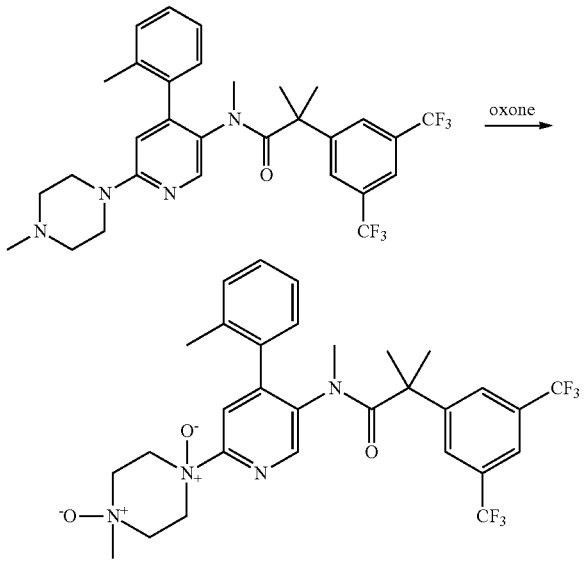
Scheme 3



To a solution of 5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-2-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridine 1-oxide (3 g, 5.05 mmol) and $NaHCO_3$ (0.354 g, 12.66 mmol) in 60 mL of MeOH and 15 mL of H_2O were added potassium monopersulfate triple salt (1.62 g, 26.25 mmol) at room temperature during 15 min. After stirring for 4 hrs at room temperature under N_2 atmosphere, the reaction mixture was concentrated in vacuo and purified by flash chromatography (eluent: MeOH). The product was dissolved into DCM, the formed solid was filtered off, and the solution was concentrated under reduced pressure to afford 1.77 g 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-1-oxido-4-(o-tolyl)pyridin-2-yl)-1-methylpiperazine 1-oxide as a white solid (Yield: 57.4%). 1HNMR (CDCl3, 400 MHz) δ 8.06 (s, 1H), 7.78 (s, 1H), 7.60 (s, 2H), 7.37~7.20 (m, 4H), 6.81 (s, 1H), 3.89 (s, 2H), 3.74 (m, 4H), 3.31 (m, 5H), 2.48 (s, 3H), 2.18 (s, 3H), 1.36 (s, 6H).

Synthesis of 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide

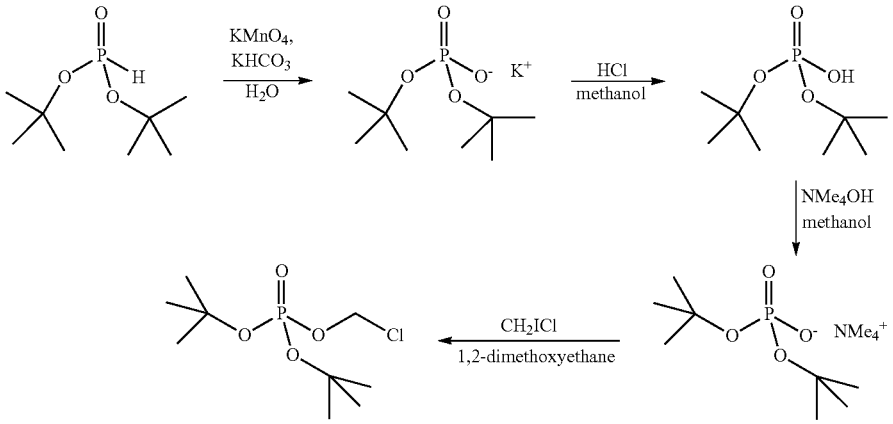
Scheme 4



To the solution of 2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide (11.1 g, 19.2 mmol) in 75 ml of Methanol was added sodium bicarbonate (3.38 g, 40.3 mmol) dissolved in 20 ml of water. Then Oxone (14.75 g, 48.0 mmol) was added to the stirred solution at room temperature in 3-4 portions. The suspension was heated for 4 h at 50° C. After filtration of the salts (washed with 3×8 ml of methanol), the solvent has been evaporated under reduced pressure and substituted by DCM (30 ml). The organic phase was washed with water (5×30 ml), dried over Na_2SO_4, filtered, concentrated and purified by precipitation in toluene to afford 9.3 g 1-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-4-methylpiperazine 1,4-dioxide as a white solid (Yield: 80%). ^{1}H-NMR (CDCl3, 400 MHz, at 333K) δ 8.27 (s, 2H), 7.75 (s, 1H), 7.63 (s, 2H), 7.26~7.19 (m, 2H), 7.14 (t, 1H, J=7.4 Hz), 7.09 (d, 1H, J=7.4 Hz), 4.93 (t, 2H, J=11.6 Hz), 4.70 (t, 2H, J=11.6 Hz), 4.12 (d, 2H, J=10.7 Hz), 3.84 (s, 3H), 3.50 (d, 2H, J=10.3 Hz), 2.47 (s, 3H), 2.12 (s, 3H), 1.40 (s, 6H).

Synthesis (A) of di-tert-butyl (chloromethyl) phosphate

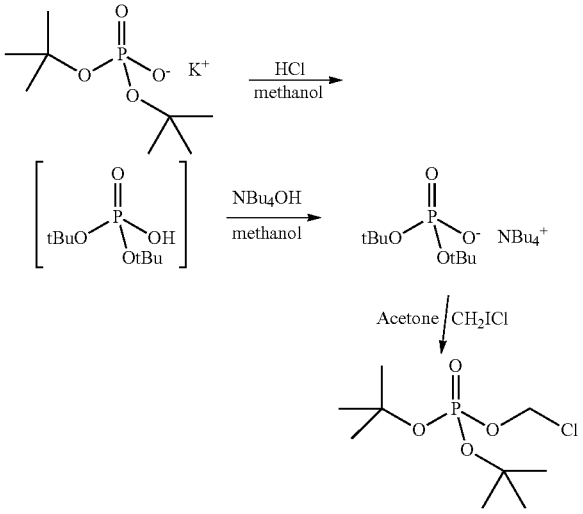
Scheme 5



Di-tert-butyl phospohite (40.36 mmole) was combined with potassium bicarbonate (24.22 mmole) in 35 ml of water. The solution was stirred in an ice bath and potassium permanganate (28.25 mmole) was added in three equal portions over one hour's time. The reaction as then allowed to continue at room temperature for an additional half hour. Decolorizing carbon (600 mg) was then incorporated as the reaction was heated to 60° C. for 15 minutes. The reaction was then vacuum filtered to remove solid magnesium dioxide. The solid was washed several times with water. The filtrate was then combined with one gram of decolorizing carbon and heated at 60° C. for an additional twenty minutes. The solution was again filtered to yield a colorless solution, which was then evaporated under vacuum to afford crude Di-tert-butyl phosphate potassium salt. Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) was dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetramethylammonium hydroxide (3.65 g, 20.14 mmole) while keeping the reaction cooled by a salt/ice bath with efficient stirring. The resulting clear solution is placed under reduced pressure to give the crude product. To the tetramethylammonium di-tert-butyl-phosphate dissolved in refluxing dimethoxyethane is then added 4.3 grams of chloroiodomethane (24.16 mmole) and stirred for 1-2 hours. The reaction is then filtered and the filtrate is placed under reduced pressure to concentrate the solution in DME. The chloromethyl di-tert-butyl phosphate 12-16% in DME is used in the synthesis of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium without further purifications (60% yield): ^{1H}NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Synthesis (B) of di-tert-butyl (chloromethyl) phosphate

Scheme 5A



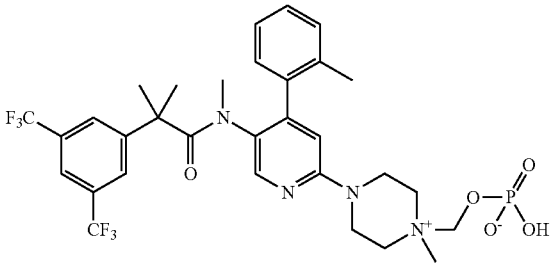
Di-tert-butyl phosphate potassium salt (5 g, 20.14 mmole) is dissolved in methanol (15 g): to this solution at 0° C. a slight excess of concentrated HCl is slowly added with efficient stirring at 0° C. The addition of acid causes the precipitation of potassium chloride. The solid is then filtered and washed with methanol. The compound in the mother liquor is then converted to the ammonium form by adding an equal molar amount of tetrabuthylammonium hydroxide 1 M in methanol (20.14 mmole) while keeping the reaction cooled at 0° C. with efficient stirring. The resulting clear solution is placed under reduced pressure to give the intermediate product. The tetrabuthylammonium di-tert-butyl-phosphate dissolved in acetone is then added dropwise to 53.3 grams of chloroiodomethane (302.1 mmole) and stirred at 40° C. for 1-2 hours. The solvent and excess of chloroiodomethane are distilled off, the reaction mass suspended

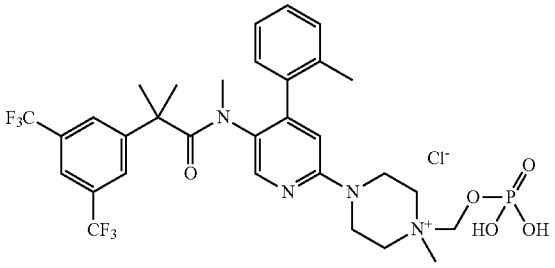
in TBME and then filtered. The filtrate is washed by a saturated solution of sodium bicarbonate and water and then placed under reduced pressure to substitute the solvent by acetone, i.e., to remove the solvent after which it is replaced with acetone. The chloromethyl di-tert-butyl phosphate 7-20% in acetone is used in the next step without further purifications (70-80% yield): ^{1}H-NMR (CD_3OD, 300 MHz) δ 1.51 (s, 12H), 5.63 (d, 2H, J=14.8). ^{31}P-NMR (CD_3OD, 300 MHz) δ −11.3 (s, 1P).

Stability studies of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium salts

In order to further improve the stability and solubility of 4-(5-(2-(3,5-bis(trifluoromethyl)phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium, a variety of its derivative salts were synthesized and tested. Their synthesis employed either a) neutralization of the dried diacid phosphate species and its corresponding base salts or b) a direct acid deprotection starting from the dried di(tert-butyl)-protected phosphate species. Neutralization was performed with L-histidine, magnesium salt, N-methyl-D-glucamine (dimeglumine), and L-lysine. Both procedures were tried in the synthesis of citric derivatives whereas with other acids the direct deprotection reaction was used. The FIGURES below show the most relevant structures.

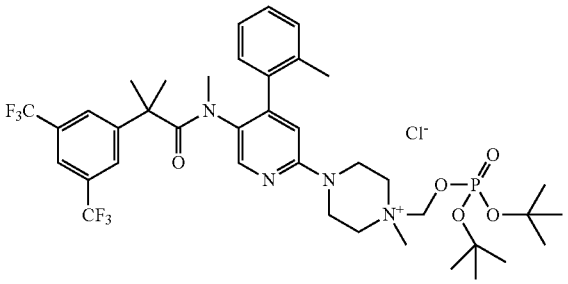
Parent Acid Species



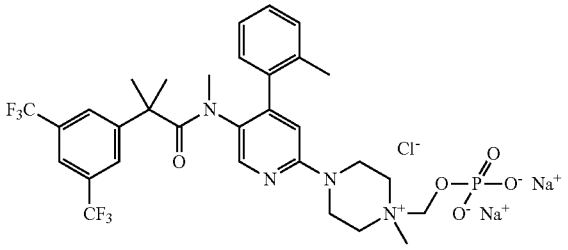


Diacid phosphate species

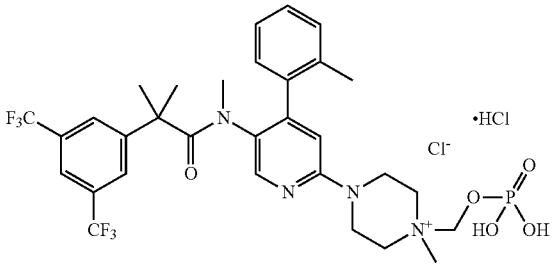
-continued



Protected phosphate species



Dibasic phosphate species



Chloride hydrochloride species

When the parent acid species was not stored in dry condition it was found to undergo over 8% degradation in the first week and over 65% degradation in the first six months. When the dried parent acid species was held at 30° C. in air it underwent 0.05 degradation in the first 7 days and at total of 7.03% degradation in six months. When the dried parent acid species was held under argon at room temperature it underwent up to 0.13% degradation in the first 7 days but then was essentially stable for six months. Results for various derivative salts are shown in Table d below.

TABLE 1

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH	L-Histidine, 2 eq.	26.6%	95.94%	Degradation: +0.70% in 6 days (in air) +0.46% in 6 days (in argon)
MeOH	$Mg(OH)_2$, 2 eq.	48.6%	94.11%	Degradation: +0.81% in 6 days (in air) +0.29% in 6 days (in argon)

TABLE 1-continued

Representative Degradation Results for Salts

Solvents	Additives	Yield %	Purity A % HPLC	Comments
MeOH + DCM, 1:1	Citric acid, 2 eq.	N.A.	94.40%	From protected species.
MeOH	1. HCl dioxane, 4 eq. 2. $Ca(OH)_2$	>90%	94.50%	From protected species.
MeOH	H_3PO_4, 85%, 2 eq.	>90%	98.81%	From protected species and retains 0.39% of that species.
MeOH	HBr, 48%, 4 eq.	84.6%	96.11%	From protected species. Product degrades rapidly.
MeOH + DCM, 1:4	CH_3SO_3H	N.A.	61.54%	From protected species. Product NOT stable: contains 32.45% decompositon species.
MeOH	NaH_2PO_4, 4 eq.	N.A.	n.d.	Only 1.27 of parent species formed. Poor reaction.
MeOH	N-methyl-D-glucamine (Meglumine), 2 eq.	N.A.	96.88%	Degradation: +0.87% in 6 days (in air) +1.52% in 11 days (in argon)
MeOH	N-methyl-D-glucamine (Meglumine), 1 eq.	>99%	97.42%	Degradation: +0.77% in 6 days (in air) +0.83% in 7 days (in argon)
MeOH + DCM, 5:2	1. NaOH, 3 eq. 2. Citric acid, 1 eq.	96.5%	97.49%	Degradation: +0.09% in 2 days (in argon) +0.59% in 89 days (in argon)
MeOH + DCM, 5:2	1. NaOH, 3 eq. 2. Fumaric acid, 1 eq.	93.8%	97.46%	Degradation: +1.95% in 14 days (in air) +1.80% in 12 days (in argon)
MeOH	L-lysine, 1 eq.	>99%	97.62%	Degradation: +0.69% in 14 days (in air) +0.48% in 12 days (in argon)

A more comprehensive showing of stability results is given in FIG. **1**, where the horizontal axis represents number of days of testing and the vertical axis represents the mass percent of degradation. Alphabetical letters are used to denote data points on the graph that correspond to degradation percentage values over time for respective salts of the same parent compound as just described above and in Table 2 below. The drawn lines correspond to general trends over periods of days for the benchmark salt (the disodium salt) and for the few salts that manifested more desirable results than the disodium salt.

TABLE 2

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
a	2 Dimeglumine	Air
b	2 Dimeglumine	Argon
c	Dimeglumine	Air
d	Dimeglumine	Argon
e	Lysine	Air
f	Lysine	Argon
g	Fumarate	Air
h	Fumarate	Argon

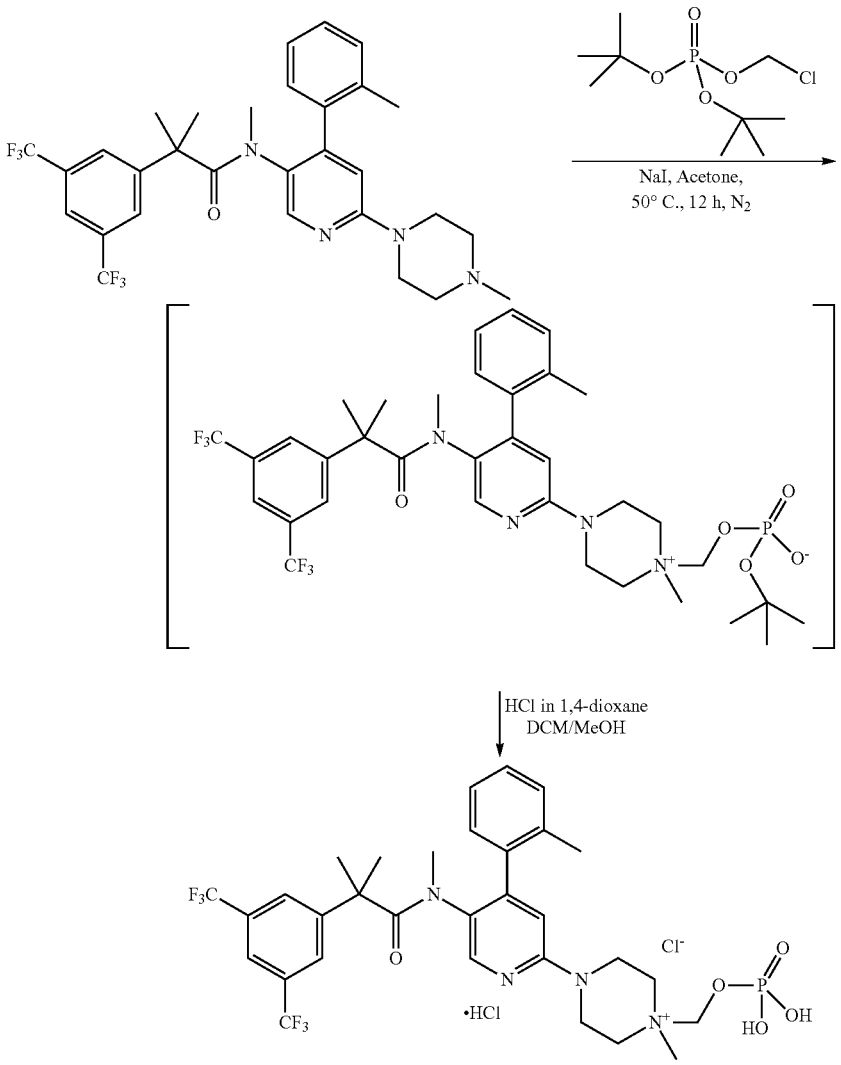
TABLE 2-continued

Identity Codes for Salts and Gases in FIG. 1.

Letter Code	Salt	Ambient gas for storage
i	Citrate	Air
j	Citrate	Argon
k	Bromide	Air
l	Bromide	Argon
m	Mesylate	Nitrogen
n	Phosphate	Air
o	Phosphate	Argon
p	Citrate	Nitrogen
q	Calcium	Air
r	Calcium	Argon
s	Chloride hydrochloride, anhydrous	Air
t	Chloride hydrochloride, anhydrous	Argon
u	Disodium salt	Air
v	Histidine	Air
w	Histidine	Argon
x	Magnesium	Air
y	Magnesium	Argon

Synthesis (A) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

Scheme 6

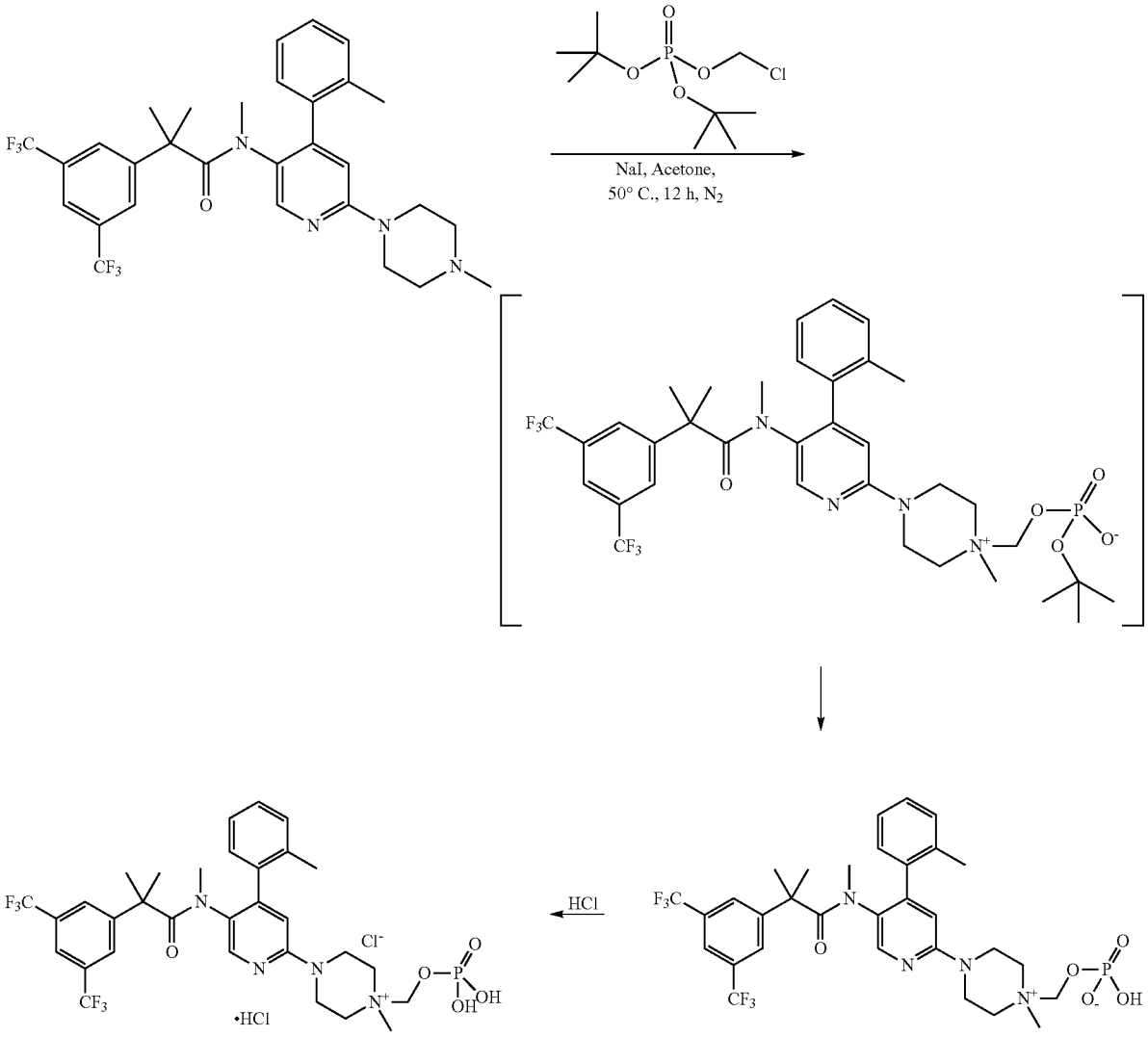


The solution of chloromethyl di-tert-butyl phosphate in DME (250 g from a 10% solution, 96.64 mmole) was evaporated under reduced pressure until the formation of pale yellow oil, dissolved then at 50° C. with 318 ml of Acetonitrile. 17.2 g (80.54 mmole) of 1,8-bis(dimethylamino)naphtalene and 46.6 g (80.54 mmole) of 2-(3,5-bis (trifluoromethyl)phenyl)-N,2-dimethyl-N-(6-(4-methylpiperazin-1-yl)-4-(o-tolyl)pyridin-3-yl)propanamide were added and the solution heated at 90° C. for at least 12 h. After the addition of 75 g of isopropylether, the precipitated crude product was cooled at room temperature, filtered and washed with acetonitrile, isopropylether/acetone, 3:1 and isopropylether, and dried under reduced pressure to afford 20-33 g of the 4-(5-{2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl]oxymethyl}piperazin-1-ium as white solid (Yield: 30-50%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.98 (s, 1H), 7.86 (s, 1H), 7.76 (s, 2H), 7.33-7.10 (m, 4H), 6.80 (s, 1H), 5.03 (d, 2H, J_{PH}=8.5 Hz), 4.52 (s, 2H), 4.13 (m, 2H), 3.83 (m, 2H), 3.69 (m, 2H), 3.52 (m. 2H), 3.23 (s, 3H), 2.53 (s, 3H), 2.18 (s, 3H), 1.46 (s, 18H), 1.39 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −5.01 (s, 1P). To 20 g (23.89 mmole) of the 4-(5-{2-[3,5-bis (trifluoromethyl)phenyl]-N,2-dimethylpropanamido}-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-{[(tert-butoxy)phosphoryl] oxymethyl}piperazin-1-ium dissolved in 180 g of methanol and 400 g of dichloromethane was added HCl 4M in dioxane (18.8 g, 71.66 mmole) and the solution was heated for 3 h at reflux. After the addition of 200 g of dioxane, DCM and methanol were distilled under reduced pressure until precipitation of the product, which was filtered and washed with isopropylether (100 g), acetone (30 g) and pentane (2×60 g). The product was finally dried under reduced pressure at 55° C. to afford 15-17 g of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride as white solid (Yield: 88-93%). ^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H),

7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J 8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

Synthesis (B) of 4-(5-(2-(3,5-bis(trifluoromethyl) phenyl)-N,2-dimethylpropanamido)-4-(o-tolyl)pyridin-2-yl)-1-methyl-1-((phosphonooxy)methyl)piperazin-1-ium chloride hydrochloride

Scheme 6A



To the solution of chloromethyl di-tert-butyl phosphate in Acetone (22.1 g from a 10% solution, 85.58 mmole), 15.5 g (103.24 mmole) of sodium iodide and 33.0 g (57.00 mmole) of netupitant were added and the solution heated at 50° C. for at 6-16 h. The precipitated salts were filtered off, the acetone distilled under reduced pressure and the crude product dissolved in 43.0 g of methanol and 43.0 g 1,4-dioxane. 12.6 g of HCl 4M in dioxane (113.85 mmole) were added, and then methanol is distilled off at 40° C. under reduced pressure. The solution is cooled at 5° C. and stirred at 5° C. for at least 2 h at 5° C. The product was isolated by filtration, purified by additional slurry in acetone (238 g), and filtered and washed with acetone (47 g) and pentane (2×72 g).

The product was finally dried under reduced pressure at 60° C. to afford 22-30 g of white-yellowish solid (Yield: 50-70%)

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.02 (s, 1H), 7.87 (s, 1H), 7.74 (s, 2H), 7.33-7.40 (m, 2H), 7.27 (m, 1H), 7.21 (s, 1H), 7.16 (d, 1H, J 8.2 Hz), 5.27 (d, 2H, J_{PH}=7.9 Hz), 4.29 (m, 2H), 4.05 (m, 2H), 3.85 (m, 2H), 3.74 (m, 2H), 3.35 (s, 3H), 2.62 (s, 3H), 2.23 (s, 3H), 1.38 (s, 6H). ^{31}P-NMR (CD_3OD, 161 MHz) δ −2.81 (t, 1P, J_{PH}=7.9 Hz).

It is to be understood that the product shown in Scheme 6A is illustrative, being just one of several permutations in which the acidic protons bond to various atoms in an equilibrium. For instance depiction of other permutations would show a proton bound to one or more of the N atoms while one or more of the 0 atoms bound to the P atom would bear an anionic charge. The invention comprises all of the molecular species within that equilibrium and the product shown in the FIGURE is intended to represent all of them in a generic fashion.

7. Evaluation of Representative Compounds of Formula (I)

i. Chemical Stability and Solubility

The chemical stability and aqueous solubility of some representative compounds of Formula (I), compared to some reference compounds, are reproduced in Table 3 below. Stability was tested according to ICH guidelines under accelerated conditions (40° C.).

TABLE 3

Chemical Stability and Solubility of Representative Compounds

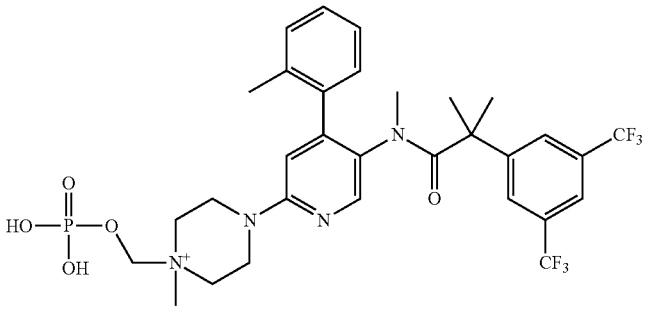
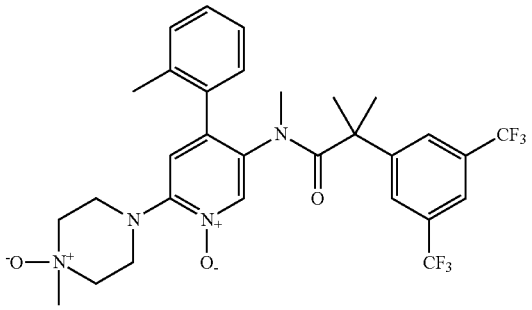
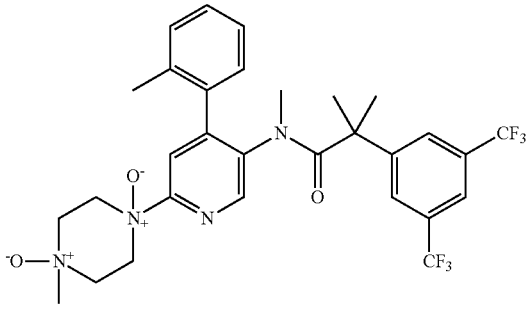
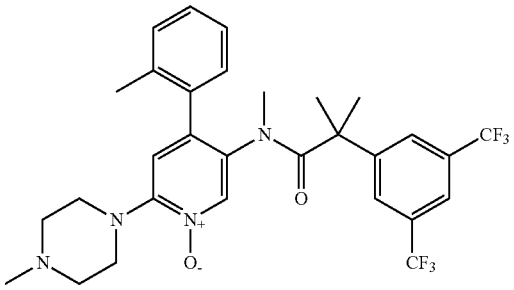
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
1		medium	10-15 mg/ml
2		high	>10 mg/ml
3		high	>10 mg/ml
4		medium	~0.6 mg/ml

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

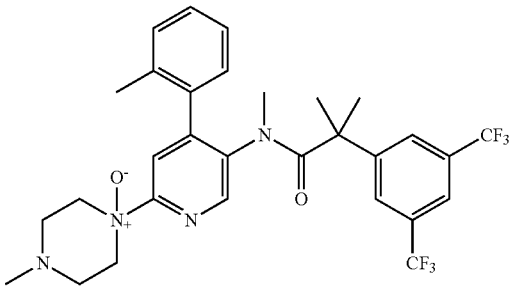
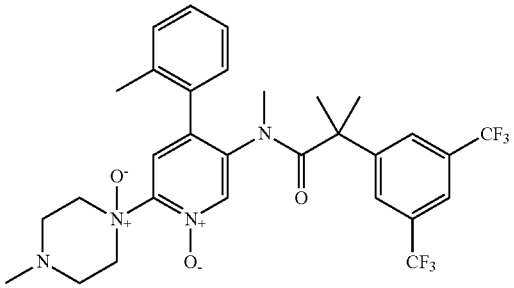
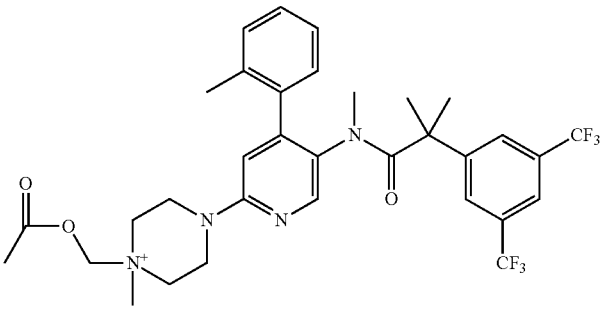
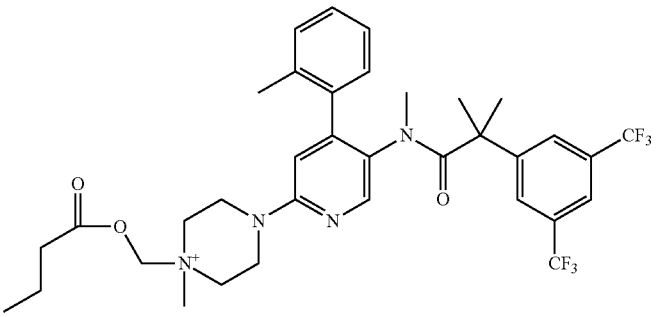
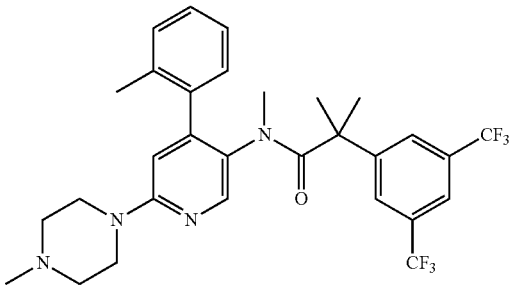
Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
5*		medium	~1 mg/ml
6		low	N/A
7		low	insoluble
8		Low	insoluble

TABLE 3-continued

Chemical Stability and Solubility of Representative Compounds

Compound No.	Compound Structure	Chemical Stability	Solubility (neutral pH)
9*			0.25

*Reference Compound

ii. Local Tolerance

In contrast to netupitant (compound no. 9 in the above table), seven-day local tolerability study of three compounds (e.g., compound nos. 1-3 of the above Table 1) on rat was conducted. All three compounds exhibited good local tolerability which is demonstrated by the below findings:

- There were minimal signs of inflammation at injection site and there was little edema;
- No later stage thrombus was found in any animal studied;
- Severity of inflammation was similar in compound and vehicle-treated animals;
- No tissue necrosis was observed in any of the tails; and
- The inflammation and palethrombus were caused by the needle injection through blood vessels.

iii. Pharmacokinetic Studies

The pharmacokinetics (PKs) study of three compounds (e.g., compound nos. 1-3 of the above Table 3), as compared to a reference compound—netupitant (orally administered), on rat and dog was conducted.

Rat PKs Study: The rats tested in the study were Wistar rats, male, body weight 220-240 g, and 5 rats per group. The dose was 10 mg/kg administered by intravenous (IV) slow bolus injection into the tail vein at a rate of 1 ml/min. The dose was administered to each animal at a dose volume of 5 ml/kg (the pre-formulation is 5% Glucose solution). Control animals received the vehicle alone. The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Before administration, rats were fasted 12 hr, water ad libitum. After 240 min time point blood was collected, rats were fed. 0.2-0.3 ml blood was collected in tubes contained EDTA/NaF as anticoagulant and stabilizer at pre-dose and at 0.05, 0.25, 0.5, 1, 2, 4, 6, 8, 24 and 48 hrs after intravenous administration. After centrifugation, plasma was removed and stored deep-frozen approximately −20° C. until analysis. Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank rat plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of rat plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of rat plasma samples. Plasma samples of time points 3, 15 and 30 min after intravenous administration were diluted 10 or 5 fold with blank rat plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Rat plasma samples were analyzed by using an API4000 MS coupled with HPLC. Repaglinide was used as internal standard. Using an internal calibration method for compound 1 of the above Table 1 or Netupitant quantitation, the LLOQ and the linear range of standard curve were 2 ng/ml and 2-2000 ng/ml, respectively.

Dog PKs Study: the dogs tested in the study were Beagle dogs, body weight 8-10 kg, and 3 male dogs per group. The four PK experiments were performed in 12 naïve dogs. The dose was 3 mg/kg administered via intravenous (IV) slow injection into the left and right cephalic or left and right saphenous veins used in rotation. The dose volume was 2 ml/kg in glucose 5% v/v solution at a fixed injection rate of 4 ml/min using an infusion pump (KDS 220, KD Scientific). The dose was administered to each animal on the basis of the most recently recorded body weight and the volume administered was recorded for each animal. Netupitant 3 mg/kg dose was tested at 2 ml/kg in vehicle (DMSO:Ethanol: Tween80 solution=5:4:1:90, v/v), dependence on its solubility. Dose was freshly prepared before each single PK experiment. Before administration, dogs were fasted 12 hr, water ad libitum. After 480 min time point blood was collected, dogs were fed. 0.5 ml blood was collected in heparinised tubes at pre-dose and at 2, 5, 15, 30 min, 1, 2, 4, 6, 8, 12, 24, 36, 48 and 72 hr after intravenous administration. Plasma samples would be kept at −20 degree till analysis. After 2 weeks washout, the same group (IV for Netupitant) was dosed Netupitant 3 mg/kg by gavage administration, the dose volume was 4 ml/kg in vehicle (Hypromellose 0.5%, Tween-80 0.1%, Sodium Chloride 0.9% in distilled water). Prepared quantification standard curve at 2, 10, 40, 100, 200, 1000 and 2000 ng/ml (diluted from methanol stock with methanol containing 1% formic acid). Aliquot 50 ul of standard solution and spiked into 50 ul of blank dog plasma samples either for standard curve or for QC samples, followed by adding 100 ul of acetonitrile (with IS). 50 ul of methanol replaced the compound standard methanol solution was used to spike 50 ul of dog plasma samples, and added 100 ul of acetonitrile (with IS), for the determination of dog plasma samples. Plasma samples of time points 2, 5, 15 and 30 min after intravenous administration were diluted 5 or 2 folds with blank dog plasma, respectively. Plasma was pre-prepared with acetonitrile using protein precipitate (PPP). Dog plasma samples were analyzed by using an API4000 MS coupled with HPLC.

MRM(+) was used to scan for Netupitant and compound nos. 1-3 of the above Table 3, respectively. Repaglinide was used as internal standard.

It was found that all three compounds, when intravenously administered at a dosage of 3 mg/kg, were efficiently converted to netupitant in rats and dogs. It was also found that compound no. 1 is bioequivalent to oral netupitant at the same dose in dog. The data of the comparative bioequivalence study is reproduced in below Table 4:

TABLE 4

Comparative Bioequivalence Studies of Netupitant and Related Compounds

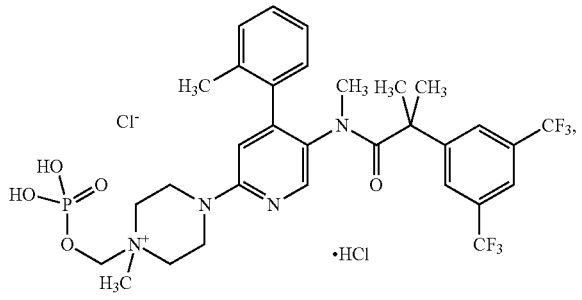
	IV			
	Compound 1	Compound 2	Compound 3	PO Netupitant*
Dose (mg/kg)	3	3	3	3
Dose (mg/kg, equivalent to netupitant)	2.31	2.84	2.84	3
Mean AUC_{0-t} (ng.min/ml)	315627	88732	192730	307285
Bio-equivalence (%)	103	29	63	

*Reference Compound

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby referenced individually and specifically for the material contained in them that is discussed in the sentence in which the reference is relied upon. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

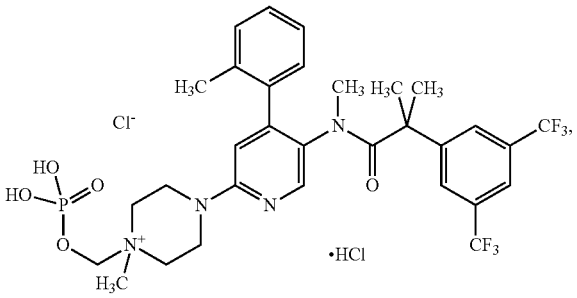
1. Fosnetupitant chloride hydrochloride having the following formula:



wherein the fosnetupitant chloride hydrochloride comprises less than 0.7% degradants via mass degradation under air and ambient conditions for a period of 80 days.

2. The fosnetupitant chloride hydrochloride of claim **1**, wherein the degradants comprise netupitant.

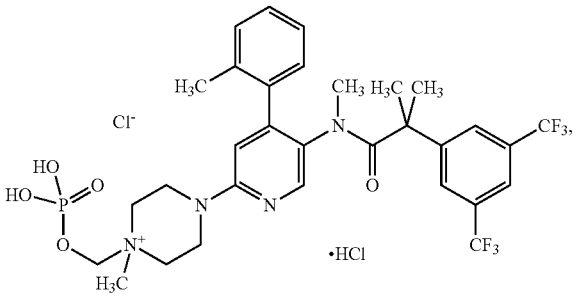
3. A pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and fosnetupitant chloride hydrochloride having the following formula:



wherein the fosnetupitant chloride hydrochloride comprises less than 0.7% degradants via mass degradation under air and ambient conditions for a period of 80 days.

4. The pharmaceutical composition of claim **3**, wherein the degradants in the fosnetupitant chloride hydrochloride comprise netupitant.

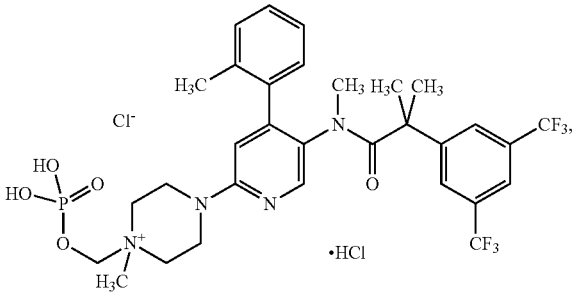
5. An injectable pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and fosnetupitant chloride hydrochloride having the following formula:



wherein the fosnetupitant chloride hydrochloride comprises less than 0.7% degradants via mass degradation under air and ambient conditions for a period of 80 days.

6. The injectable pharmaceutical composition of claim **5**, wherein the degradants in the fosnetupitant chloride hydrochloride comprise netupitant.

7. Fosnetupitant chloride hydrochloride having the following formula:

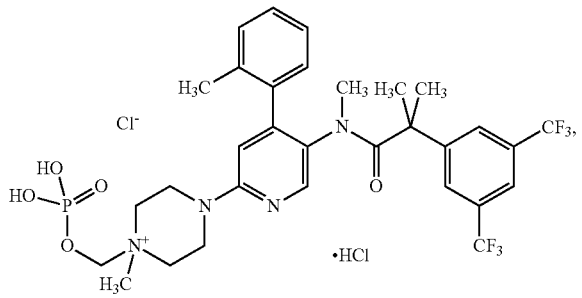


wherein the fosnetupitant chloride hydrochloride is in the form of an anhydrate; and

wherein the fosnetupitant chloride hydrochloride comprises less than 0.7% degradants via mass degradation under air and ambient conditions for a period of 80 days.

8. The fosnetupitant chloride hydrochloride of claim **7**, wherein the degradants comprise netupitant.

9. A pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and fosnetupitant chloride hydrochloride having the following formula:

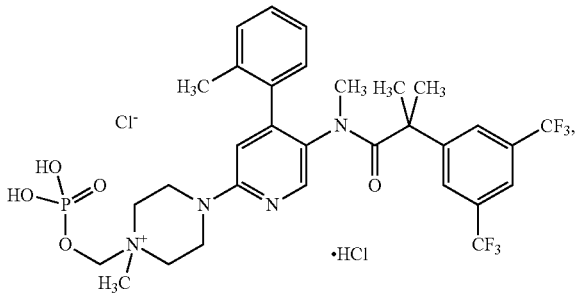


wherein the fosnetupitant chloride hydrochloride is in the form of an anhydrate; and

wherein the fosnetupitant chloride hydrochloride comprises less than 0.7% degradants via mass degradation under air and ambient conditions for a period of 80 days.

10. The pharmaceutical composition of claim **9**, wherein the degradants in the fosnetupitant chloride hydrochloride comprise netupitant.

11. An injectable pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and fosnetupitant chloride hydrochloride having the following formula:



wherein the fosnetupitant chloride hydrochloride is in the form of an anhydrate; and

wherein the fosnetupitant chloride hydrochloride comprises less than 0.7% degradants via mass degradation under air and ambient conditions for a period of 80 days.

12. The injectable pharmaceutical composition of claim **11**, wherein the degradants in the fosnetupitant chloride hydrochloride comprise netupitant.

* * * * *